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**Neuropsychological Functioning Post-Renal Transplantation: A prospective comparison
of A Steroid Avoidance and A Steroid Maintenance Protocol in Relation to Chronic
Prednisone Therapy**

by

Nikhil S. Koushik

A Dissertation

Submitted to the Faculty of Graduate Studies

Through the Department of Psychology

In Partial Fulfillment of the Requirements for

The Degree of Doctor of Philosophy at the

University of Windsor

Windsor, Ontario, Canada

2008

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ABSTRACT

Thirty-nine participants, 17 in a chronic steroid group (CS) and 22 in a steroid avoidance group (SA) were compared with regard to their cognitive performance. It was predicted that participants in the SA group would outperform those in the CS group on the domains of declarative memory and complex attention. For participants in the CS group, age and prednisone duration but not dose were predicted to significantly contribute to the score on the declarative memory composite score. Group-wise comparisons were not significant for the domains of declarative memory, complex attention, or processing speed. The CS group outperformed the SA group on the domain of simple attention. Regression analysis, for the CS group, indicated that duration of dialysis prior to transplant accounted for a significant portion of the variance in the declarative memory composite score. After controlling for months since transplant, prednisone dose also accounted for approximately 26% of the variance in the declarative memory score. Patients maintained on 5 mg of prednisone performed relatively worse than those maintained on 2.5 mg with regard to declarative memory. The clinical and theoretical significance of the findings relative to recent literature is discussed.

DEDICATION

I would like to dedicate this manuscript to my parents, Sadashiv and Aruna Koushik.

Without their loving support, nothing I have achieved in my life would have been possible.

I am deeply indebted to them for nurturing my ideas, hopes, and dreams and for serving as a sounding board to my “constant whining”.

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I. INTRODUCTION

The management and treatment of patients with Chronic Kidney Disease (CKD) has evolved tremendously over the past 30 years (Pliskin, Kolbasa, Hart, & Umans, 2001). During that time, there has been a concurrent progression of knowledge about the neuropsychological correlates of CKD. Investigations conducted during the 1960s and 1970s examined the neurocognitive effects of uremia (blood poisoning) and chronic renal (relating to the kidneys) failure. Studies in the late 1970s and 1980s focused on the neurocognitive sequelae of chronic hemodialysis (HD) and peritoneal dialysis (PD) (Pliskin et al., 2001). As renal transplantation has become a more viable option for many patients with CKD, there is an interest in the neurocognitive effects of this procedure.

In accordance with the recent interest in the neurocognitive sequelae of renal transplantation, the prospective investigation that is presented in this paper was carried out with the specific objective of examining the cognitive impact of long-term, low-dose prednisone. The clinical importance of the investigation is highlighted by the fact that several patient groups may be exposed to long-term, low-dose corticosteroids including recipients of solid organ transplantation and those with certain rheumatic conditions. In the present study, two groups of post renal transplant recipients on steroid avoidance or maintenance protocols were compared with regard to their performances on the cognitive domains of declarative memory, simple attention, complex attention and processing speed. The relative contribution of patient age, duration of prednisone and dose of prednisone to predicting variance in a declarative memory score for participants in the steroid maintenance condition was also examined. Prior to describing the investigation, the literature on cognitive functioning as it relates to CKD and steroid therapy is reviewed.

II. REVIEW OF THE LITERATURE

The objective of this portion of the paper is to provide the reader with information regarding neuropsychological functioning in CKD. More specifically, the majority of the introduction will focus on neuropsychological functioning as it pertains to immunosuppressive medications (specifically steroids) utilized to manage patients who are post-renal transplant. A list of terms that are used throughout this paper is presented in the Appendix A.

In order to present information in a structured and logical manner, this portion of the paper is divided into six sections. Information about basic renal physiology and measures of renal function is presented in Section One. Section Two covers the classification, epidemiology, and common etiologies of CKD. Dialysis and the neuropsychological correlates of dialysis are covered in Section Three. Section Four examines transplantation and the neuropsychological correlates of transplantation. Section Five introduces the reader to post-transplant immunosuppression and the related neuropsychological findings. Section Six provides the reader with a relatively detailed overview of the neuropsychological literature as it relates to a specific component of the immunosuppressive regimen, namely corticosteroids.

Section One- Basic Renal Physiology and Measures of Renal Function

The kidneys are bean-shaped organs, each about the size of a fist, located near the middle of the back, just below the rib cage. Each kidney is composed of approximately one million nephrons (the functional unit of the kidney). Each nephron in turn is composed of a compact package of interconnected capillary loops (glomeruli) surrounded by a capsule (Bowman's capsule), which is attached to a series of long

tubules (Mohanram & Toto, 2005). Substances are filtered from blood that enters the glomeruli. Re-absorption of nutrients from the filtrate occurs in the glomeruli and the tubules. The filtrate is then excreted as urine, and the blood is returned to circulation through the renal veins. Together, the glomeruli and tubules compose the working mass of the kidneys (Danovitch, 2005; Mohanram & Toto, 2005).

In general, the kidneys are responsible for regulating urinary output relative to dietary salt and water intake (Eaton & Pooler, 2004). The input of water into our bodies is extremely variable because many of the foods and beverages we consume are comprised, to varying degrees, of water. The kidneys respond by adjusting the output of water in the urine, thereby maintaining constant total body water content (Lieberthal & Nigam, 2000). Minerals such as sodium, potassium, and magnesium are also, to varying degrees, components of the foods and drinks we consume. As with water, our kidneys excrete these minerals at a highly variable rate that, in sum, matches input.

In addition to the liquids and foods we consume, our bodies are continuously forming end-products as a result of metabolism. In most cases these end-products serve no function and are harmful at high concentrations. Removal of urea (by-product of protein metabolism), uric acid (by-product of nucleic acid metabolism), creatinine (by-product of muscle metabolism) and other metabolites is one of the foremost functions of the kidneys (Lieberthal & Nigam, 2000). Failure of the kidneys to remove these substances from the blood results in waste buildup, leading eventually to uremia. In its advanced stages uremia is characterized by fatigue, anorexia, nausea, drowsiness, impaired concentration, and generalized nonspecific complaints, that may progress to frank encephalopathy with possible seizures (Pliskin et al., 2001).

Blood pressure depends substantially on blood volume that is in turn regulated by the kidneys' maintenance of sodium and water balance. Thus, the kidneys participate in regulation of blood pressure through volume control (Eaton & Pooler, 2004).

The kidneys serve a variety of important endocrine functions. Erythropoietin is a peptide hormone that is involved in the control of erythrocyte (red blood cell) production by the bone marrow. The kidneys produce the vast majority of erythropoietin, although the liver also secretes small amounts (Lee et al., 2004). The stimulus for secretion of erythropoietin is a reduction of partial pressure of oxygen in the kidneys. This can occur, for example, in anemia (a condition in which blood is deficient in erythrocytes, hemoglobin, or total blood volume), arterial hypoxia (deficiency of oxygen in arterial blood), and inadequate renal blood flow. In these situations, erythropoietin stimulates the bone marrow to increase production of erythrocytes (Marsh et al., 1991; Pliskin et al., 2001).

The active form of vitamin D (1, 25-dihydroxyvitamin D₃) is produced in the kidneys. Production of vitamin D in turn helps to regulate calcium, phosphorus and parathyroid hormone levels (Burrows-Hudson, 2005). Finally, the kidneys are responsible to a large degree for gluconeogenesis (synthesis of glucose from non-carbohydrate sources such as protein and triglycerides) (Eaton & Pooler, 2004).

The kidneys serve a wide array of functions, all facilitated by their capacity to transport water and solutes between the blood flowing through the kidneys and the lumina of the tubules (Lieberthal & Nigam, 2000). Substances that are in excess, or are not needed, are eventually excreted in the urine. Thus, the kidney is the organ chiefly responsible for the maintenance of liquid homeostasis within the human body.

Clinically, several techniques are used to assess renal function. The variety of measurement techniques become more important when considering that CKD is commonly silent in the early stages (Mohanram & Toto, 2005; Pliskin et al., 2001). Glomerular Filtration Rate (GFR) is one of the most commonly used measures of global renal function. It is a measure of the efficiency with which the kidneys filter and clear substances from the blood (Harvey, 2003). Operationally, it is defined as the clearance

by filtration of a marker from the plasma by the kidneys, usually within a specified amount of time (Burrows-Hudson, 2005; El Nahas & Bello, 2005; Harvey, 2003). An ideal marker is one that is freely filtered, not protein bound, readily available clinically, and safe and inexpensive (Burrows-Hudson, 2005; Mohanram & Toto, 2005). Theoretically, although there are many such markers available, only markers that are typically used in clinical settings will be discussed in this paper.

The two most popular endogenous markers of kidney function are serum creatinine and blood urea nitrogen. Creatinine is a non-toxic by-product of muscle metabolism (Kidney/Disease Outcome Quality Initiative (K/DOQI), 2002). Serum creatinine is used as an endogenous marker because its rate of production is relatively stable (roughly 10-20 mg creatinine/kg body weight per day), it is not protein bound, and is freely filtered (Pliskin et al., 2001). Serum creatinine is influenced by age, body weight, and gender as all three of these are related to muscle mass. Recent formulas take these factors into account when calculating GFR based on serum creatinine (K/DOQI, 2002; El Nahas & Bello, 2005). Another indirect gauge of GFR involves prediction based on creatinine clearance. In this method, the amount of creatinine excreted in the urine is compared to the level in the plasma over a 24-hour period. However, because portions of the tubules also secrete a small amount of creatinine, creatinine clearance frequently leads to an overestimation of GFR (Levey et al., 2003). However, GFR estimation from 24-hour creatinine clearance is frequently used for people with exceptional diets (i.e., vegetarians, those taking creatine supplements). Serum creatinine combined with modification equations that control for age, mass, and gender appears to be the most commonly used clinical method for calculation of GFR (Burrows-Hudson, 2005; K/DOQI, 2002; Levey et al., 2003).

Blood urea nitrogen is a by-product of protein metabolism that serves as a useful clinical marker of renal function (K/DOQI, 2002). Blood urea nitrogen, which is normally

approximately 10-20 mg/dl, is prone to inaccuracy depending on the patient's protein intake and breakdown, which in turn is dependent on diet, liver function, and renal function. Furthermore, while blood urea nitrogen increases with falling GFR (thus providing a measure of renal integrity), it is also selectively retained whenever blood flow to the kidneys is compromised, as in the case of dehydration or congestive heart failure (K/DOQI, 2002). Therefore, the degree of blood urea nitrogen elevation is typically an imperfect marker of renal failure because it depends on non-GFR related factors. However, measurement of blood urea nitrogen clearance (the ratio of its excretion rate to its concentration in the blood) typically provides a more conservative estimate of GFR than does creatinine clearance (Mohanram & Toto, 2005).

Microalbuminuria and Proteinuria

Although both serum creatinine and blood urea nitrogen provide useful measures for estimating GFR and overall renal integrity in normal individuals, there is some evidence to indicate that they may not be sensitive enough when screening for CKD (K/DOQI, 2002; El Nahas & Bello, 2005; Levey et al., 2003). This is particularly true in the early stages, when renal function may be modestly compromised (Bishop, 2001; Burrows-Hudson, 2005). Microalbuminuria is the leakage of small amounts of a blood protein called albumin into the urine, and serves as a more sensitive indicator of early renal dysfunction. As kidney function worsens, the amount of albumin and other proteins in the urine increases due to a reduced ability to filter substances, leading to proteinuria (K/DOQI, 2002). Albuminuria and subsequently proteinuria can both be detected with the use of an inexpensive dipstick urinalysis. If this test indicates the presence of CKD, management of the disease progresses to monitoring GFR (Burrows-Hudson, 2005; Pliskin et al., 2001).

Section Two- CKD, Classification, Epidemiology and Etiology

Classification

CKD classification has been improved by the adoption of the five tiered scheme recently proposed by the National Kidney Foundation in its Kidney Disease Outcome Quality Initiative (K/DOQI, 2002). The adoption of a universally accepted classification scheme and associated terminology has allowed comparisons to be drawn across various investigations. Prior to the publication of this scheme, communication between scientists was hampered by the usage of various combinations of expressions referring to the same idea. The scheme proposed by the National Kidney Foundation is presented in Table 1 and has several elements.

First, the National Kidney Foundation has adopted the term CKD to refer to the entire spectrum of disease that follows the initiation of kidney damage (Stages 1 and 2). In their scheme CKD is defined as either kidney damage (as measured by increased proteinuria, biopsy, or structural imaging) and/or decreased kidney function (as measured by $GFR < 60 \text{ mL/min/1.73m}^2$ body surface area (bsa)) for three or more months (Levey et al., 2003).

Second, the five tiered model ranges from occult kidney damage with well preserved renal function (Stage 1), down to the level of renal failure requiring replacement therapy (Stage 5). Notably, the National Kidney Foundation guidelines point out that kidney failure is not synonymous with end-stage renal disease. End-stage renal disease is an administrative term used to denote that a patient is being treated with renal-replacement therapy (i.e., dialysis or transplantation). This is the condition for payment for health care by the Medicare End-stage Renal Disease Program. As such, the category of end-stage renal disease does not include patients with kidney failure who are not being treated with dialysis or transplantation (Ganesh, Hulbert-Shearon, Port, Eagle, & Stack, 2003; Levey et al., 2003).

Third, according to the proposed criteria, a documented GFR below 60 mL/min/1.73m² bsa, may by itself fulfill the definition of CKD without additional evidence of underlying kidney damage. This cutoff for GFR was selected because it represents a loss of half or more of the adult level of normal kidney function (Levey et al., 2003). It is below this level that associated complications (e.g., uremia, anemia) typically occur (Eustace & Coresh, 2005). Therefore, patients with a GFR between 60 and 89, without evident kidney disease, are defined as having decreased GFR with or without associated hypertension rather than CKD. This approach avoids potentially misclassifying otherwise healthy elderly people with decreased GFRs without associated evidence of kidney failure. Furthermore, it also helps to identify individuals who are potentially at risk of developing CKD as a consequence of their lower baseline GFR (Knight, Oesthun, Teng, Lazarus, & Curhan, 2003; Schaubel, Morrison, Desmeules, Parsons, & Fenton, 1998; Stengel et al., 2003).

Fourth, stage five, which is denoted when GFR dips below 15 mL/min per 1.73m² bsa, typically indicates the need for initiation of renal replacement therapy. In the United States approximately 98% of patients begin dialysis when their GFR drops below this level (Atkins, 2005; Jones, 2003).

Overall, the staging system proposed by the National Kidney Foundation focuses primarily on the severity of kidney dysfunction rather than on diagnostic considerations. As such, it acts to complement and in no way replaces traditional classification schemes based on etiology. In fact, several investigations suggest that CKD stage, as outlined in the guidelines set forth by the National Kidney Foundation, is an excellent measure of severity and an accurate predictor of the risk of comorbidity and complications (El Nahas & Bello, 2005; Knight et al., 2003; Levey, et al., 2003). Limitations to this classification scheme have been pointed out. GFR tends to decline with age. However, little is known about the causes of this decline, which may be due to CKD. If so, it may be more

appropriate to classify individuals with GFRs between 60 and 89 mL/min/1.73m² bsa without apparent markers of kidney damage as having CKD rather than “decreased GFR” (Jones, 2003; Levey, et al., 2003; Obrador, Pereira, & Kausz, 2002). The GFR cut-off values for stages three to five were selected based on limited data with respect to the relationship between complications and level of GFR. The K/DOQI work group has called for further investigations to enable a refinement of these cutoffs.

Epidemiology

The prevalence and incidence of end-stage renal disease is rising worldwide as reflected in the increasing numbers of individuals on renal replacement therapy (Atkins, 2005; Schaubel, et al., 1998). There is substantial evidence to suggest, at least in the case of North America, that this is a result of the aging population and the pandemic of Type II Diabetes (El Nahas & Bello, 2005; Himmelfarb, 2002; Knight et al., 2003). The number of patients in the End-stage Renal Disease Medicare funded program in the United States increased from approximately 10,000 beneficiaries in 1973 to 86,354 in 1983, to 340,261 in 1999 (Obrador et al., 2002). Furthermore, in the United States, the number of people with kidney failure who are treated with dialysis and transplantation is projected to increase from approximately 340,000 currently to 650,000 by the year 2010 (United States Renal Data Systems, (USRDS), 2000). There appears to be some worldwide variability in the rates of renal replacement therapy, with higher rates in developed countries. Specifically, between the years 2000 and 2003 incidence rates of end-stage renal disease were 100, 135, and 330 new patients per million of the population in the United Kingdom, Europe, and the United States respectively (El Nahas & Bello, 2005). These rates appear to be much higher than in less developed countries such as India, presumably because of the high cost of renal replacement therapy. Furthermore, disparities in the incidence of end-stage renal disease within and between more developed countries are likely to reflect the varying racial and ethnic mixes. For

example, in the United States and Australia the annual incidence of end-stage renal disease is substantially lower in white (94 and 250 per million/year respectively) than in African-American (982 per million/year) people (El Nahas & Bello, 2005). The number of patients with end-stage renal disease likely underestimates the entire burden of CKD, because individuals in the earlier stages (i.e., 1 to 3) may often go undiagnosed or misdiagnosed (Himelfarb, 2002; Lysaght, 2002).

In the United States, the most comprehensive examination of the epidemiology of CKD was conducted through the Third National Health and Nutrition Examination Survey (NHANES-III) (Jones, 2003). NHANES-III was a cross-sectional survey of the US civilian non-institutionalized population that was implemented in two nationally representative phases. Overall, more than 29,000 persons aged six months and older participated in NHANES-III (Jones, 2003). In general, the findings of the NHANES-III study implied that up to 11% of the United States general adult population (19 million people) could have some degree of CKD, including more than 8 million individuals with GFRs less than 60 mL/min/1.73m² bsa. The analysis also estimated that 5.9 million people could have stage one CKD with normal renal function (Coresh, Astor, & Greene, 2003). One of the drawbacks associated with NHANES-III included serum creatinine measurements that were taken at one point in time, which makes interpretation of some results difficult. However, it provides some evidence suggesting that the problem of CKD and subsequent end-stage renal disease, in the United States, is on the rise. Other screening surveys of population representative samples in Australia, Japan, and Europe have identified between 6 and 11 percent of individuals in those countries as having some degree of CKD (Chadban, Briganti, & Kerr, 2003; Glassock, 2004; Stengel et al., 2003).

Etiology

CKD risk factors are broken down into several categories. The two most relevant to the present discussion are susceptibility factors and initiation factors. The former are those that increase the likelihood of kidney damage (e.g., old-age, family history of CKD), while the latter are those that cause kidney damage (e.g., hypertension, diabetes).

Diabetes mellitus is the leading cause of CKD in the United States, and patients with diabetes account for approximately one-third of all cases of end-stage renal disease (Ritz & Orth, 1999; Shumway & Gambert, 2002). Both Type 1 (formerly insulin-dependent diabetes mellitus) and Type 2 (formerly non-insulin-dependent diabetes mellitus) diabetes can lead to diabetic nephropathy (microvascular complication leading to deteriorating renal function). However, it is estimated that the global epidemic of Type 2 diabetes will be chiefly responsible for the global increase in CKD in the years to come (Caramori & Mauer, 2003; Glassock, 2004). Clinically, the first evidence of nephropathy in both disease subtypes is the presence of microalbuminuria. This is invariably accompanied by the presence of an elevated GFR to more than 120 mL/min/1.73 m² bsa. After 5-10 years, some patients will progress to macroalbuminuria with no initial change in GFR. However, if no intervention is administered at this point, GFR will continue to decline leading to end-stage renal disease (Dahm & Cooper, 2002; Harvey, 2003). The progression of the disease may be more pronounced in individuals with Type 2 diabetes because they frequently have had the condition for some time before a diagnosis is rendered (Shumway & Gambert, 2002). For example, a higher proportion of individuals with Type 2 diabetes are found to have microalbuminuria and overt nephropathy at the time they are diagnosed (Nesbitt, 2004). Furthermore, in 50% of patients with Type 2 diabetes, hypertension is noted before microalbuminuria (National High Blood Pressure Education Program, 2003).

Several current theories exist as to how the hyperglycemic state produced by diabetes results in diabetic nephropathy; however, many investigations illustrate that the structural change that occurs in diabetes is a thickening of the glomerular basement membrane resulting in the subsequent inability to efficiently regulate the filtration of various substances such as albumin (Dahm & Cooper, 2002; Harvey, 2003; Ritz & Orth, 1999; Shumway & Gambert, 2002). Although there is currently no cure for diabetic nephropathy, measures such as strict blood pressure control, exercise, and glycemic control can slow the progression of the disease (Caramon & Mauer, 2003; Harvey, 2003).

Hypertension is unique in that it is both a cause and a consequence of CKD (Adamczak, Zeier, Dikow, & Ritz, 2002; Flack et al., 2003; Luft, 2004). Hypertension can be defined as abnormally high arterial blood pressure (consistently greater than 140/90 millimeters of mercury) (Pease, 2002). Data suggest that hypertension is linked to CKD and proteinuria, as well as kidney disease related mortality (Martins, Tareen, & Norris, 2002; Muirhead, 2001). Approximately 85% of persons with CKD (Stages 3 to 5) have hypertension (Jones, 2003; Pontremoli et al., 2002).

The kidney has its own mechanism to regulate blood pressure, through the release of a hormone called renin. The release of renin triggers a series of events in several body systems eventuating in the conversion of the protein angiotensin I to angiotensin II by angiotensin converting enzyme. Angiotensin II causes, amongst other things, vasoconstriction of the blood vessels, and increased blood pressure (Adamczak, et al., 2002). Since CKD affects blood perfusion within the glomeruli, it is frequently accompanied, to some extent, by hypertension.

There are two theories regarding the pathophysiology of hypertension in nephropathy. The first states that chronic hypertension results in a narrowing of pre-glomerular afferent arteries and arterioles, causing reduced blood flow to the glomeruli

and the subsequent release of renin, resulting in increased blood pressure (Adamczak et al., 2002). A second possibility is that chronic hypertension results in sclerosis (hardening) of some glomeruli, causing increased pressure in the remaining glomeruli. To compensate for reduced renal function, there is increased blood flow to the remaining glomeruli and subsequent hyperfiltration, glomerular hypertension, and progressive damage (Adamczak et al., 2002; Fervenza, 2005). These two mechanisms are not mutually exclusive and likely occur, to some extent, simultaneously. Once CKD is initiated, there is significant evidence to suggest that if uncontrolled, hypertension acts to progressively worsen the course of the disease through increased proteinuria due to reduced filtration capacity (Luft, 2004). Several studies have illustrated that hypertensive diabetics (Types 1 and 2), and people with CKD and proteinuria lose kidney function faster than those without proteinuria (Klein et. al., 1999; Luft, 2004; Maschio, Marcantoni, & Bernich, 1999). Although there is no cure for hypertension in CKD, strict blood pressure control, exercise, and dietary modifications are necessary to reduce its impact. Furthermore, the efficacy of antihypertensive medications in reducing the progression of microalbuminuria to subsequent proteinuria has been well documented (Burrows, 2005; Dahm & Cooper, 2002; Glasscock, 2004).

A smaller group of individuals experience CKD due to autoimmune diseases. The two autoimmune diseases that most commonly lead to the development of CKD are Systemic Lupus Erythematosus and Systemic Vasculitis. Systemic Lupus Erythematosus is a disorder in which the body begins to produce antibodies against its own tissues and organs. Common points of attack are the skin and various internal organs such as the kidneys (Cameron, 1997). The most common complication of Systemic Lupus Erythematosus leading to CKD is Lupus Nephritis. In Lupus Nephritis there is an accumulation of antibodies in the kidney that subsequently lead to damage of various internal kidney structures. Many investigators have reviewed the number of

patients with Systemic Lupus Erythematosus who develop renal diseases, with overall estimates ranging from 25% to 65% (Cameron, 1997; O'Callaghan, 2004). The nature of the renal disease caused by Systemic Lupus Erythematosus is highly variable and can result from several disease processes, all implicating the accumulation of antibodies in various internal kidney structures but varying in severity. For example, tubular interstitial disease involves an inflammation of the renal tubules and the spaces between these tubules and the glomeruli. Patients with Lupus Nephritis may experience renal associated problems similar to those of other CKD patients such as hypertension. Management of the renal diseases in these patients requires a consideration of the severity of the disease (Korbert, Lewis, Schwartz, et. al., 2000).

The Systemic Vasculitides are a group of rare diseases thought to be caused by immune-mediated inflammation and necrosis of blood vessels, leading to eventual occlusion and subsequent necrosis of the tissues fed by these vessels (Cunnard & Kelly, 2003). Examples of diseases in this category include: Wegener's Granulomatosis, Giant Cell Arteritis, and Microscopic Polyangiitis. Estimates of the incidence of primary vasculitic disease are approximately 7-15 new cases per million per year (Watts, Carruthers, & Scott, 1995). Treatment of the various Systemic Vasculitides ranges from the use of Cyclophosphamide in patients with mild to moderate CKD to plasma exchange in patients with disease severe enough to warrant HD (Pusey, Rees, & Evans, 1996). A range of other conditions, including scleroderma and rheumatoid arthritis, can also be associated with renal pathology. However, renal involvement in such conditions is not necessarily a common problem (Cunard & Kelly, 2003; O'Callaghan, 2004).

Currently, there are two treatment options for the person with severe CKD. The first of these is dialysis, subclassified further as either HD or PD. Dialysis is still the first treatment of choice worldwide for those with end-stage renal disease. More recently, kidney transplantation has become a viable treatment option. These two treatment

options and associated neuropsychological sequelae will be reviewed in the following sections.

Section Three- Dialysis and its Neuropsychological Correlates

Dialysis

Dialysis continues to be the most highly utilized renal replacement therapy worldwide. Strictly speaking, it is defined as the passage of molecules in solution by diffusion across a semipermeable membrane (Yeun & Depner, 2005). Essential elements of the process include a solvent that contains dissolved solutes and a membrane that contains pores through which some or all of the solutes move by diffusion. There are two types of dialysis, HD and PD.

The basic procedure in HD involves the removal of excess water and solutes from blood that is passed along a semipermeable membrane within a dialysis filter, as blood is passed through an extracorporeal circuit (Nesrallah, Blake, & Mendelssohn, 2005). Dialysis fluid circulates on the other side of this large surface area membrane, allowing wastes to flow down their concentration gradients out of the blood and needed molecules, such as calcium, to be delivered to the patient (Pliskin et al., 2001).

Adequate HD is that level of treatment that will minimize long-term mortality and morbidity, be fiscally efficient, and most of all, provide patients the best possible quality of life (Leypoldt, 2005). Currently, the most widely accepted measurement for HD adequacy is (Kt/V) where K is the total cleared volume of urea, t is the total time of dialysis, and V is the patient's total body water (Gotch & Sargent, 1985). HD is considered adequate when Kt/V is at least 1.2 (Gotch & Sargent, 1985; N/KDOQI, 2002). HD sessions typically take place three times per week and last for 3 to 4 hours. HD is sometimes referred to as intermittent dialysis, a label emphasizing the accumulation of toxins that may take place between sessions (Pliskin et al., 2001).

On the other hand, PD utilizes the patient's own highly vascular peritoneal membrane as the semipermeable dialyzer and blood supply, with sterile dialysis fluid installed directly into the abdominal cavity (Gokal & Mallick, 1999). Solutes, including uremic wastes, potassium, and acids diffuse along their concentration gradients into this fluid. Water is also transferred along this gradient. The net result is a translocation of solute and fluid from blood into the dialysate. The dialysate is changed at regular intervals so that the solutes are removed and the concentration and osmotic gradients may be restored (Nesrallah, Blake, & Mendelssohn, 2005).

There are several types of PD including, Continuous Ambulatory PD (CAPD), Continuous Cycling PD and Nocturnal Intermittent PD. The latter two are both considered types of automated PD because dialysate solution is drained from the abdomen through the aid of a machine rather than through manual means as in CAPD (Gokal & Mallick, 1999). CAPD is the most common type of PD, and as the name implies, the patient performs his or her own exchanges, which usually take place every 4-6 hours. CAPD is considered adequate when Kt/V is at least 2.0 (K/DOQI, 2002). In continuous cycling PD, an automated cycler is used to perform three to five exchanges over-night while the patient sleeps. A further exchange is performed in the morning after which the dialysate stays in the abdomen the entire day (called the dwell time). Nocturnal intermittent PD uses an automated cycler to perform somewhere between six and eight exchanges over the course of the night with full daytime dwells (i.e., no daytime exchanges at all) (Gokal & Mallick, 1999). The type of PD a patient receives depends on several medical factors, such as the amount of residual renal function the patient has, and the permeability of his/her peritoneum. For example, nocturnal intermittent PD may be suitable for a patient who has substantial residual renal function and high peritoneal membrane permeability (Nesrallah, Blake, & Mendelssohn, 2005).

Neuropsychological Correlates of Dialysis

A number of investigations have established the presence of mild to moderate neuropsychological dysfunction in the areas of general intelligence, memory and attention, or processing speed in groups of people with chronic renal failure and progressive uremia (Hart, 1983; Murawski, 1975; Teschan et al., 1979).

Likewise, neuropsychological functioning after the initiation of dialysis has also been examined extensively (Gilli & DeBastiani, 1983; Hagberg, 1973; Jackson, Warrington, Roe & Baker, 1987; McKee et al., 1982; Osberg, Meares, McKee, & Burnett, 1982). Interpretation of many of the early studies is hindered by several methodological limitations. First, many investigations failed to take into account adequate dialysis delivery, because standards for minimal dialysis prescription were presented only in 1985 (Gotch & Sargent, 1985). As such, it is difficult to ascertain whether cognitive deficits obtained in these investigations were an artifact of residual uremia. Second, comparison across studies examining neuropsychological functioning in HD is hampered because the timing of neuropsychological testing in relation to dialysis was variable. That is, some investigators tested subjects just prior to HD, a time when their uremic state was likely worst, whereas in other studies they were tested at various times after dialysis (e.g., immediately after, several hours post-HD, 24 hours post-HD). Third, when examining neuropsychological functioning in areas such as attention and memory, many investigators failed to account for significant confounding variables such as education (i.e., failed to match groups for years of education). Lastly, only a few of these studies considered other potentially relevant demographic factors such as race and age.

Due to the plethora of methodological flaws, many of the early investigations will not be dealt with directly, but will be mentioned in the context of more recent studies. In general, neuropsychological investigations of patients on dialysis have examined

cognitive functioning in the areas of general intelligence, memory, and attention and processing speed.

Studies Comparing Dialysis Patients to Matched Controls

Wolcott et al. (1988) examined whether dialysis modality may be an independent factor in predicting the level of functioning of chronic dialysis patients. To that end, they compared neurocognitive functioning in 17 pairs of CAPD and chronic HD patients matched for sex, age, education, duration of dialysis and diabetic status. They also compared the performance of these two dialysis groups to a reference group of age-matched controls. At the time of the study, all participants had been receiving dialysis for at least 6 months. Adequate dialysis was defined as a Kt/V between 0.8 and 1.2 for patients receiving HD, and four to five two-liter exchanges and regular (i.e., weekly) monitoring for patients receiving CAPD. The neuropsychological assessment included measures of attention and processing speed (i.e., number cancellation, Symbol Digit Modalities, Trail-Making Test- Part A (TMTA)), memory (Rey Auditory Verbal Learning Test (RAVLT)), and executive functioning (Trail-Making Test- Part B (TMTB)).

The performance of both dialysis groups was mildly impaired across all measures when compared to the reference group of age-matched controls. Patients receiving CAPD consistently outperformed those on chronic HD across the majority of measures. Although this investigation employed relatively rigorous exclusionary criteria, a serious methodological drawback was that patients receiving HD were tested just prior to dialysis, a time when their uremic status was likely highest, and their neuropsychological performance most compromised.

Churchill et al. (1992) conducted a double-blind single-crossover study to investigate the effect of high-flux HD on neuropsychological functioning. Participants included a group of stable chronic HD patients who had been on dialysis for at least 3 months and matched controls. Each patient received at least 2 months of conventional

HD at a Kt/V greater than 1.0. Each patient was then randomly allocated to receive either conventional or high-flux treatment for 4 months, after which they received the alternate treatment for 4 months. High-flux HD involves the use of dialysis membranes with the capacity to remove higher weight molecular substances. The rationale is that if a greater refinement is achieved in the ability to filter substances, this may lead to fewer uremic symptoms, and, in this case, improved cognitive functioning. The neuropsychological battery was chosen to evaluate attention and concentration (Wechsler Adult Intelligence Scale-Revised (WAIS-R)- Digit Span subtest, Corsi Block Span, TMTA and the Continuous Performance Test), verbal fluency (Controlled Oral Word Association and Animal Naming), visuomotor speed (Grooved Pegboard Test and WAIS-R Digit Symbol Coding), constructional ability (WAIS-R Block Design, Complex Figure Drawing, and Clock Drawing), memory (Wechsler Memory Scale (WMS)- Logical Memory and Paired associates subtests, Benton designs and the Recurring Figures Test) and executive functioning (TMTB, Stroop Test).

For the purposes of the study, none of the 23 neuropsychological variables showed statistically significant treatment related changes. The performance of both the conventional and high-flux groups on the selected WAIS-R subtests suggested a low-average range of intellectual functioning compared to published norms. For both groups of dialysis patients other performance deficits, where noted, were most marked on measures of attention and concentration such as the Continuous Performance Test and Corsi Block Span, perceptual motor speed (e.g., Digit Symbol Coding) and cognitive flexibility (e.g., TMTB).

More recently, Pliskin, Yurk, Ho, and Umans (1996) sought to determine whether well-dialyzed, well-nourished and medically stable end-stage renal disease patients would exhibit neuropsychological dysfunction compared to demographically matched medical controls. Their sample comprised 16 well-dialyzed (i.e., M Kt/V urea= 1.46)

patients with end-stage renal disease who had been receiving HD for at least 6 months, and 12 age-and education-matched controls. All participants demonstrated low-average intellectual functioning and had an average of 10 years of education. All patients were tested on a single mid-week, post-dialysis day with a comprehensive neuropsychological battery that included tests of memory, attention, language, and motor skills.

Findings revealed few significant differences on any of the neuropsychological domains assessed. Indeed, both groups demonstrated mildly impaired neuropsychological performance overall. The patients with end-stage renal disease performed more poorly on two of the three test conditions (i.e., word and color) of the Stroop Test relative to controls; however, there were no significant differences on other measures of attention or processing speed.

In a follow-up investigation of attention and mental processing speed, Umans and Pliskin (1998) administered a battery of six attentional measures (Stroop Test, TMTA, TMTB, WAIS-R Digit Span Subtest, Paced Auditory Serial Addition Test (PASAT), Gordon Diagnostic System and the Continuous Performance Test) to 10 stable chronic HD patients ($M Kt/V = 1.35$) and 10 medical controls with normal renal function. As in their previous investigation, they found that the patients receiving HD performed more poorly than controls on the Stroop Colour and Word conditions. Although these differences did not reach statistical significance, they were of a magnitude that might be of functional importance (i.e., clinically relevant in this patient population). There were no significant group differences on any other measures. The authors note that the generalizability of their results is hindered by their relatively small sample size.

Given the frequent occurrence of vascular disease in patients receiving HD, Pereira and colleagues hypothesized that the cognitive performance of the patients receiving HD in their sample would reflect a subcortical pattern of performance. The

sample included 25 HD patients with Mini Mental State Exam scores greater than 24 and no history of cerebrovascular disease. The performance of the patients on measures of verbal list-learning (Wechsler Memory Scale- Third Edition (WMS-III) verbal list-learning), attention and processing speed (Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol Coding, TMTA and TMTB), and visual-construction (WAIS-III- Block Design) were compared to published norms. All HD recipients were tested an hour into a session of HD (Pereira et al., 2007).

In relation to published normative data, significant deficits for patients receiving HD were found on the digit symbol coding subtest, the block design subtest, and the TMTA and TMTB tests, within the context of preserved performances with regard to the retention and recognition scores from the verbal list-learning task. The authors conclude that, in accordance with their hypothesis, the pattern of performance is suggestive of subcortical dysfunction; however, they fail to explicate how their findings are consistent with such a pattern (Pereira et al., 2007).

Other Relevant Investigations

Griva et al. (2003) examined the neuropsychological functioning of 145 patients with end-stage renal disease. Their sample consisted of 77 patients receiving HD and 68 receiving PD (CAPD= 45; Automated PD= 23) matched for age and education. All patients were adequately dialyzed and had been receiving dialysis for at least 6 months at the time of the study. Both groups completed two neuropsychological assessments over a 24-hr interval. Patients receiving HD were assessed 2 hr prior to their regularly scheduled dialysis session (Time 1) and then 24 hrs after the end of their last dialysis session (Time 2). Patients receiving PD followed the same regimen. Furthermore, each participant was tested at almost the same time on each testing occasion and alternate forms of tests were used on second testing sessions. The neuropsychological assessment consisted of measures of attention and processing speed (i.e., TMTA,

Symbol Digit Modalities Test), memory (i.e., RAVLT, Benton Visual Retention Test) and fine motor dexterity (i.e., Grooved Pegboard Test). When averaged over the two time-periods there were no statistically significant differences on any measures across dialysis modality. That is, when scores were averaged out, the subjects in both the HD and the PD groups demonstrated approximately equivalent scores on all the neuropsychological measures. While the performance of the patients receiving HD was significantly better at Time 2 than Time 1 on all neuropsychological measures, patients receiving PD exhibited stable performances across both assessments. An important finding from the investigation was that absolute levels of cognitive function were associated with adequacy of dialysis. Specifically, adequacy of dialysis (i.e., Kt/V) predicted scores on tests of attention and concentration. The major methodological limitation with the study was the absence of a control group to which the performance of both dialysis groups could be compared. The failure to find significant cognitive differences between groups of patients receiving HD versus PD, when patients receiving HD are tested at the appropriate time (i.e., 24-48 hrs after a session) has been demonstrated in another recent investigation (Williams, Sklar, Burright, & Donovan, 2004).

Given the literature that demonstrates an association between CKD and anemia, presumably due to the fact that the kidney produces the vast majority of erythropoietin, Marsh et al. (1991) studied the effect of rHuEPO (synthetic form of erythropoietin) treatment on the efficiency of cognitive functioning using neuropsychological measures. Participants included 24 patients who had all been receiving HD for at least 5 months at the time of the study. All had some degree of anemia as measured by hematocrit (test for number of red blood cells) level ($M= 23.7$). Dialysis was prescribed to achieve a Kt/V of 1.0-1.2, which was kept constant over the course of the study. The neuropsychological assessment evaluated attention and processing speed (Symbol Digit

Modalities Test, TMTB), memory (RAVLT) and verbal fluency (The Controlled Oral Word Association Test). All participants were administered neuropsychological tests at three times, first before rHuEPO treatment (Pre-T), after three months of treatment (T3) when hematocrit values had stabilized at criterion level of 32% or above, and after 12 months (T12). For each evaluation, subjects were studied on a day following a regularly scheduled and completed dialysis run as closely as possible to 24-hrs after the completion of the last dialysis session. Only 14 of the original 24 participants completed all three neuropsychological testing sessions; however, 19 completed at least two.

Mean scores from the four neuropsychological measures showed improvement with rHuEPO treatment. After three months of treatment, the Symbol Digit Modalities Test score increase was significant, while those for the RAVLT and the Controlled Oral Word Association Test approached statistical significance. After 12 months of treatment, the TMTB time to completion decreased significantly (i.e., improvement), and the Symbol Digit Modalities Test showed further improvement, but the RAVLT and Controlled Oral Word Association Test scores again failed to show significant change. One has to wonder about the possibility of practice effects as a confounding factor in the interpretation of results. However, the improvement in the neurocognitive functioning of individuals receiving HD after the treatment of anemia has been replicated by others (Grimm et. al., 1990; Lee et al., 2004).

Conclusions

Many of the investigations conducted prior to the 1990s were poorly designed. The majority failed to consider the adequacy of dialysis delivery. Furthermore, they failed to consider the timing of test administration in relation to dialysis, failed to account for anemia in dialysis patients, and neglected to consider demographic variables such as education and race. Although many of these early investigations found deficits in neuropsychological functioning in the domains of learning, memory, attention and

concentration (Gilli & DeBastiani, 1983; Hagberg, 1974; Hart, 1983; McKee et al., 1982; Teschan et al., 1979; Ryan, Souheaver, & DeWolfe, 1981), the results are uninterpretable due to the methodological drawbacks. Recent investigations applying more rigorous methodology appear to suggest at least some evidence for overall mildly impaired neurocognitive functioning in patients receiving HD compared to controls. Specifically, several studies suggest compromised functioning in at least some aspects of attention, and this appears, at the current time, to be the most robust finding across investigations. This may be attributable to the fact that HD is not a perfect proxy for transplantation and restores only a fraction of renal function to individuals (i.e., they may still experience residual uremia). Furthermore, compliance with dialysis regimens is an ongoing difficulty that is faced by many dialysis clinics (Danovitch, 2005). The few studies conducted thus far that have examined the cognitive functioning of patients receiving HD versus PD have found minimal differences, especially when the testing of individuals receiving HD is conducted at the appropriate time (i.e., not right before dialysis). There remains a need for well-controlled longitudinal investigations examining the long-term neuropsychological implications of treatment with either HD or PD.

Section Four- Transplantation and its Neuropsychological Correlates

Transplantation

Transplantation is currently the ideal treatment modality for patients with end-stage renal disease, as most patients enjoy an improved quality of life post-renal transplantation (Fiebiger, Mitterbauer, & Oberbauer, 2004; Lazzaretti, Mulinari, & Rasia, 2004). The major obstacle to this treatment continues to be the shortage of available organs (Danovitch, 2005; Young & Gaston, 2000). The two types of renal transplantation are cadaveric (i.e., deceased donor) and living donor. Currently, cadaveric transplants account for a small majority of kidney transplants, at least in the

United States. Between 1987 and 2004 cadaveric transplants accounted for more than half (i.e., 60%) of all kidney transplants, with the remainder being from living donors (Danovitch, 2005). There are numerous medical criteria that are considered when selecting potential recipients for transplantation and all recipients are subject to several screening procedures to determine suitability (e.g., age, psychiatric history, body mass index). Although there are no strict contraindications to transplantation, the presence of indicators in any of these domains may further complicate the procedure (Magee, 2005). The potential recipient also has to be tested for ABO blood type and Human Leukocyte Antigen tissue typing must be done. The latter involves the important transplant genes of the Major Histocompatibility Complex. In humans, the Major Histocompatibility Complex is known as the Human Leukocyte Antigen. It is the compatibility of the genes of the Major Histocompatibility Complex, between donor (living or dead) and recipient, as well as blood type compatibility, which dictates, from an immunological perspective, whether the organ transplantation can be done (Magee, 2005; Suthanthiram & Strom, 1994).

Once transplanted, the recipient's body will recognize the transplanted organ as foreign and try to destroy it. In immunologic terms, the organ is analogous to the common cold virus (antigen), which the body will try to destroy. Therefore, transplanted patients have to be on a lifelong regimen of immunosuppression that typically involves several agents aimed at different points in the recipient's immune response. Although this regimen varies across transplant centers, it usually involves the use of a monoclonal antibody (i.e., thymoglobulin, OKT3) and mycophenolate mofetil in the first 10 days after transplantation to prevent acute rejection (i.e., destruction of the organ in the first 3 to 6 months post-transplantation). This is followed by a combination of medications that typically include at least one calcineurin inhibitor (i.e., tacrolimus or cyclosporine), an antimetabolite (i.e., mycophenolate mofetil) and possibly corticosteroids (i.e.,

prednisone) (Kirk, Mannon, Swanson, & Hale, 2005). All these agents are used for various immunological purposes. For example, calcineurin inhibitors, such as tacrolimus, are typically used for long-term (i.e., maintenance immunosuppression).

Although corticosteroids have historically been a vital element of the post-transplant immunosuppressive regimen, a growing trend in the literature is for patients to be maintained without corticosteroids post-transplantation (Danovitch, 2005). This is primarily due to the variety of deleterious effects these drugs have on the human body. They have been implicated in causing muscular problems, cataract formation, growth retardation, and body disfiguration and contributing to the development of diabetes mellitus, arterial hypertension, and metabolic dysregulation (Lerut, 2003).

An important distinction is that between so called steroid-withdrawal, and steroid-avoidance protocols. The former involves a tapering of the initial post-transplant corticosteroid dose over the course of several months, whereas the latter involves corticosteroid discontinuation after only 3 to 4 days post-transplantation (Prasad, Nash, McFarlane, & Zaltzman, 2002). As it stands, neither of these protocols is considered for patients thought to be at high immunologic risk (Hricick, 2005; Vincenti, 2004). The potential benefits of both these protocols have to be weighed against the associated risk of graft rejection. Both of these protocols have been associated with higher incidences of graft rejection, particularly steroid withdrawal (Danovitch, 2005; Pascual, Theruvath, Kawai, Rubin, & Cosimi, 2002). Evidence indicates that, in general, the use of corticosteroids in solid organ transplant has not declined substantially over the last 5 years (Hricick, 2005; Kaufman et al., 2004; Vincenti, 2004).

Neuropsychological Correlates of Transplantation

There is a scarcity of investigations examining neuropsychological functioning in adults post-renal transplantation (Pliskin et al., 2001). Most of the existing literature

addresses the neuropsychological ramifications of long-term immunosuppression that is inherent to transplantation; however, this will be discussed in the next section.

Teschner et al. (1979) examined neuropsychological functioning in three groups of patients in various phases of chronic renal failure. Group 1 (N= 72) consisted of patients with varying degrees of CKD as indicated by serum creatinine concentrations that varied from 2 to 29 mg/dl. None of these patients were on dialysis at the time of the investigation. Patients in Group 2 (N= 77) were all on chronic HD for at least 60 days. It should be noted that the neuropsychological assessment of these patients was conducted immediately prior to dialysis. Patients in Group 3 (N=18) were all at least 45 days post-transplant. Finally, data was also obtained from a fourth group of control participants (N=45). Neuropsychological measures were chosen to assess attention and memory and included the Trail-Making Test, Auditory Short-term Memory Test, Continuous Memory Test, Answer Recognition Test, and the Choice Reaction Time Test.

Across measures, the performance of the transplanted patients was comparable to the normal control subjects. However, the investigators did not provide data comparing the performance of the post-transplant patients to either the patients with CKD, or the dialyzed patients. Furthermore, it is unclear as to how the investigators assessed adequate dialysis delivery.

Kramer et al. (1996) studied the neuropsychological performance of 15 patients on chronic HD, who were tested again approximately 15 months after transplantation. The neuropsychological measures utilized included the TMTA and the Mini Mental State Exam. Findings indicated a trend towards improvement after transplantation on both the TMTA and the Mini Mental State Exam; however, this improvement did not reach statistical significance. The authors acknowledged that their test battery was relatively

circumscribed. Furthermore, it is unclear as to how the investigators controlled for dialysis related factors such as uremia and adequacy of delivery.

In a recent investigation, Griva et al. (2004) examined neuropsychological functioning in transplant recipients in relation to normative data and a concurrently assessed group of pre-transplant patients on dialysis. To that end, they administered the TMTA, TMTB, Symbol Digit Modalities (written and oral), RAVLT (total recall trials 1-5, delayed recall), and the Grooved Pegboard Test to 117 transplant patients, and 167 dialysis patients (68 PD; 77 HD). Dialysis dosing was considered adequate if Kt/V met or exceeded the UK Renal Association Guidelines as follows; for CAPD, a Kt/V of 1.70; for automated PD (without daytime dwell) a Kt/V of 2.0 and for HD a Kt/V of 1.20. All patients were tested at approximately the same time of day.

The performance of transplant recipients was significantly better than that of dialysis patients on the TMTA, Symbol Digit Modalities Test, RAVLT total recall trials 1-5 and the RAVLT delayed recall, and no worse than that of age-referenced controls (Griva et al., 2004). The investigators acknowledge that slightly more transplant recipients scored 1 SD below their age-referenced norms than anticipated in a normal distribution. The study requires replication utilizing a group of closely matched healthy volunteers.

In one of the most definitive studies to date, Griva et al. (2006) used a longitudinal design to evaluate neuropsychological functioning before and after renal transplantation. Twenty-eight medically stable patients were assessed before and again 6 months after renal transplantation using a test battery comprised of tests of attention and executive function (TMTA, TMTB, Symbol-Digit Modalities Test), memory and learning (RAVLT, Benton Visual Retention Test), and psychomotor functioning (Grooved Pegboard Test). All patients were dialyzed adequately prior to transplantation. Neuropsychological testing during HD was conducted 24-hrs after their last session. The second testing occurred 6 months after renal transplantation. Results revealed

significant improvements pre- to post- test on measures of verbal and visual memory (i.e., RAVLT, BVRT) (Griva et al., 2006). Although there was a trend towards improved performance on the other cognitive measures none of these differences approached statistical significance.

Gelb, Shapiro, Hill, & Thornton (2007) examined the neuropsychological functioning of renal transplant recipients in relation to a group of healthy controls. Transplant recipients had all maintained a successful graft for at least six months. Neuropsychological measures included tests of verbal memory (California Verbal Learning Test- trials 1-5, and 20-minute delayed recall) and attention and executive functioning (Trail-making test and the Colour-Word Interference Test from the Delis Kaplan Executive Function System). Results revealed that the healthy controls outperformed the transplant recipients with regard to the Colour-Word Interference Test and the California Verbal Learning Test. The authors conclude that the findings suggest the presence of memory and executive functioning difficulties post-renal transplantation relative to healthy controls.

Conclusions

There is some evidence to suggest improved neuropsychological functioning post- renal transplantation. This improvement appears most prominent on tests of verbal and visual memory, and attention and processing speed. Relative to healthy controls, there is evidence of ongoing difficulties with aspects of memory and executive functioning. Replication of these investigations is necessary to confirm the validity of their findings.

Section Five- Neuropsychological Correlates of Post-Transplant

Immunosuppression

Neuropsychological Correlates of Post-Transplant Immunosuppression

An immunosuppressive regimen is a necessary requirement post-transplantation to ensure engrafting, as well as to prevent acute and chronic rejection. Given the wide variety of immunosuppressive medications utilized (mentioned above), and their differential impacts upon the immune system, it is no surprise that there has been some interest in the neurocognitive sequelae of exposure to these drugs. Although neurologic complications due to lifelong immunosuppression, such as frank encephalopathy and leukoencephalopathy, have been well documented (Benetoli et al., 2004; Christe, 1994; Cohen & Raps, 1995; Craven, 1991), there is a paucity of literature on the associated neurocognitive sequelae of such encephalopathy, in relation to immunosuppressive agents.

DiMartini et al. (1991) conducted a randomized, nonblinded controlled trial of tacrolimus versus cyclosporine in liver transplant recipients. Cognitive outcome was assessed via the Mini Mental State Exam, TMTA and TMTB, and the Dementia Rating Scale. Although there was no significant statistical difference on the Mini Mental State Exam between the two groups, the researchers found a significantly positive correlation between plasma levels of cyclosporine and tacrolimus and total time to complete the TMTB. This study utilized a very small sample size (N=24). Furthermore, the researchers failed to include an age and education matched control group, and to equate the two treatment groups for age and education.

More recently, Griva et al. (2004) examined the association between immunosuppressive medication and neuropsychological outcomes using a sample of renal transplant recipients. Participants included 117 post-transplant recipients. Multivariate analysis revealed non-significant group differences on all of the

neuropsychological test scores between the cyclosporine and tacrolimus treated groups including; TMTA, TMTB, Symbol Digit Modalities Test, RAVLT- (total recall trials 1-5), and The Grooved Pegboard Test. However, univariate analyses demonstrated that increasing plasma levels of cyclosporine correlated significantly with poorer neuropsychological test performance as assessed by the Grooved Pegboard Test, Symbol Digit Modalities Test-Oral, TMTA, and TMTB. In contrast, serum levels of tacrolimus were unrelated to the neuropsychological test scores. The researchers conclude that, although different types of immunosuppressive medication appear to have comparable effects on neurocognitive performance, increasing serum levels of cyclosporine appear to be associated with poorer neuropsychological performance, particularly on measures of fine motor dexterity, processing speed, and executive functioning.

In an attempt to investigate the relationship between other post-transplant medications and cognitive functioning, Bermond et al. (2005) examined the memory functioning of 52 renal transplant recipients in relation to prednisone using the Rey 15-Word Test. Results revealed a significant effect for delayed recall on the 15-Word Test indicating a memory impairment specific to delayed recall in their sample of post-renal transplant patients receiving prednisone. However, the researchers did not indicate how they determined the presence of a deficit.

Conclusions

There is some evidence suggesting poorer neuropsychological performance in post-transplant patients managed on cyclosporine. Modest evidence also suggests a negative impact of prednisone on delayed declarative memory. Further exploration into the links between immunosuppression and neuropsychological performance is required. In contrast to the limited research on the relationship of some immunosuppressants to cognition (i.e., cyclosporine and tacrolimus), there is an enormous body of literature

examining the neuropsychological functioning of individuals on corticosteroids. Although most of this literature exists outside the realm of organ transplantation, many of the principles established through the study of healthy controls and various other clinical populations (i.e., rheumatoid arthritis) may be used to predict the potential effects of corticosteroids in transplant recipients. A review of this literature will now be provided.

Section Six- Corticosteroids and Cognition

The Physiology of Stress

Corticosteroids are released endogenously as a result of the stress response. Therefore, the basic physiology of the stress response will be reviewed. The concept of stress as a physiological and neuroendocrine process can be credited primarily to the work of Hans Selye, an Austrian born endocrinologist. Selye studied the effects of prolonged stress, such as cold, or injection of poisons, on animals. He observed an invariable pattern of physical response that he termed the "General Adaptation Syndrome" that can be broken down into three stages. In the first, or alarm stage, the initial shock of the stress is followed by a mobilization of forces within the organism to mitigate against the shock. After a few days of exposure to the stress, the organism seems to adapt to the stress and its physiology returns to normal (in reality this is just the immune system working overtime to meet the demands of the stressor). Selye termed this second stage resistance. Finally, in the last phase termed exhaustion, the organism's acquired adaptation to the stressful situation is lost, resulting in a series of physiological changes that may eventuate in death (Marshall & Garakani, 2002). Selye did not overlook the nervous-neuroendocrine multihormonal complexity of the stress response; however, this clarification had to await more detailed biological knowledge (Angelucci, 2000). He made many important conceptual connections along these lines that aided in furthering the knowledge about the endocrine substrates of stress. For

example, he proposed that the adrenal hormones were the final operants of the adaptive mechanism. He further predicted the anti-inflammatory role of endogenous adrenocorticotrophic hormone (ACTH) and cortisone (Angelucci, 2000).

The endocrine response to stress is complex but involves two main processes. The primary glands involved include the pituitary and the adrenal glands with the hypothalamus acting as the moderating factor. In the first pathway termed the Sympathetic-Adrenal-Medullary axis, or SAM, stressful environmental stimuli cause direct activation of the adrenal medulla through sympathetic nervous stimulation. This triggers the adrenal medulla to release the catecholamines epinephrine and norepinephrine. Approximately ten minutes later there is activation of a second, more indirect axis termed the Hypothalamic-Pituitary-Adrenal-Cortical system, or HPA, which causes release of corticotropin releasing factor by the hypothalamus into the blood. Corticotropin releasing factor stimulates the anterior pituitary to release ACTH, which travels through the bloodstream to stimulate the adrenal cortex to produce corticosteroids (i.e., mineralocorticoids, MCs such as aldosterone and glucocorticoids, GCs such as cortisol) (Marshall, & Garakani, 2002). Both these axes are closed systems, with the catecholamines eventually feeding back to various portions of the sympathetic nervous system to help turn off the SAM axis, while cortisol eventually feeds back to the hypothalamus to help shut-off the HPA axis (Angelucci, 2000).

The end-products produced through both these pathways prepare the individual to cope with stress. However, it is generally thought that the SAM is triggered first and aids in a rapid response (i.e., prepare for the fight or flight response), while the HPA allows for a more longstanding response to stress (Marshall & Garakani, 2002; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000).

Glucocorticoids and the Brain

The interest in the effects of GCs, such as cortisol, on cognition was initiated with the publication of Bruce McEwen's seminal paper "Selective retention of corticosterone by limbic structure in rat brain" (McEwen, Weiss, & Schwartz, 1968). This paper demonstrated that the rodent brain was able to recognize hormones, particularly corticosteroids, the hormones involved in the endocrine response to stress. The investigators further reported that the brain region showing the highest density of receptors for corticosteroids was the hippocampus, a brain region significantly involved in learning and memory. It was with this finding that the stress-hippocampus link was born. It has been kept alive for the last three decades by a variety of findings confirming the significant impact of stress hormones (either endogenous or exogenous) on hippocampal structure and/or function and on animal and human learning and memory (Lupien & Lepage, 2001; Lupien et al., 1997; Margarinos & McEwen, 1995; Mason, 1968).

The knowledge of the effects of corticosteroids on the brain was furthered with the discovery of two types of corticosteroid receptors in the rodent brain, a discovery made by Roussel-Unclaf in the early 1980s (Lupien, et al., 2002a). In humans and primates, Type I receptors, or mineralocorticoid receptors (MRs), are found primarily in the limbic system with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. They have an affinity for endogenous corticosteroids six to ten times that of Type II receptors. Type II receptors, or glucocorticoid receptors (GRs), are found in both subcortical and cortical structures, including the hippocampus, but have a preferential distribution in the prefrontal cortex (Lupien & Lepage, 2001; McEwen, Gould, & Sakai, 1992). Many of the studies in the human literature have examined the impact of exogenous synthetic GCs on cognition and specifically memory. Some have used dexamethasone, while others have used

prednisone or hydrocortisone. It should be noted that there is variability in the potency and duration of effect of the various synthetic GCs. This should be kept in mind when trying to draw comparisons across the various studies in the human literature (Plihal, Krug, Pietrowsky, Fehm, & Born, 1996).

Memory Terminology

Since much of the research on GCs and cognition has focused on memory, a brief note concerning terminology relevant to this domain is warranted.

Neuropsychologists have conceptualized memory as a multi-component process, with taxonomies generally including two types of memory, namely declarative and non-declarative. The former is the memory for long-term knowledge that can be called to consciousness and reflected on, alternatively known as explicit memory. The latter is knowledge that can influence thought and behaviour without necessary conscious involvement, also termed implicit memory (Squire, 2004). Declarative memory is that which is referred to when the term “memory” is used in everyday language and is further broken down into memory for facts (i.e., semantic memory) and events (i.e., episodic memory). Several lines of evidence with humans have revealed an association between structures within the medial temporal lobe, and particularly the hippocampus, and declarative memory (Bayley, & Squire, 2003; Squire, 2004; Tulving, & Markowitsch, 1997). The general classification of medial temporal lobe structures includes those in the “hippocampus proper,” such as the dentate gyrus, Ammon’s horn, and the subiculum, versus the “perihippocampal region” comprising the entorhinal cortex, perirhinal cortex and the parahippocampal gyrus (Tulving & Markowitsch, 1997).

Memory processing has been broken down into different stages including encoding (i.e., acquisition), consolidation, and retrieval (Squire, 2004). Memory decay can occur as a result of the temporal gradient between the stimulus presentation and recall, or due to interference from information presented before the material to be

recalled (i.e., proactive interference) or after the material to be recalled (i.e., retroactive interference) (Squire, 2004). Generally, neuropsychological tests within this domain are constructed to parse out some of these subcomponents. For example, standardized neuropsychological verbal list-learning tasks typically comprise a variety of indices. For example, a comparison of the number of words remembered on the first presentation of the list (free recall) versus the recognition component may assist in discriminating encoding from retrieval problems. In fact, the pattern of recall on the first trial itself may shed light on the relative efficiency of these processes.

Most of the investigations that will be reviewed with regard to GCs and memory in humans have utilized standardized neuropsychological measures of memory (e.g., Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Wolkowitz et al., 1990), while others have utilized experimental paradigms (e.g., Lupien et al., 2002b; Lupien, Gillin, & Hauger, 1999). The latter are more common in the animal literature where investigators typically rely on spatial memory paradigms, such as the Morris Water Maze (e.g., Luine, Spencer, & McEwen, 1993; Roozendaal, 2000). Furthermore, with animals, investigators have attempted to parse out the various subcomponent processes of memory by controlling the timing of administration of the GC under consideration.

Animal Studies

Several studies have examined the effects of exogenous GCs on various aspects of learning and memory using animal models. This literature will be reviewed, as some of the findings are applicable to the human literature.

GRs, and to a lesser degree MRs, in the hippocampus may be lost as a function of aging. Both hippocampal damage and hippocampal receptor loss is associated with learning impairments. Several studies have suggested a strong association between elevated cortisol levels and hippocampal and/or GR damage (DeKloet, Oitzl, & Joels, 1999; DeLeon et al., 1997; Lupien & LePage, 2001). Sapolsky, Krey, and McEwen

(1986) argued that, in rats, both elevated levels of GCs, in the short-term as well as cumulative exposure to normal concentrations of the hormone, lead to hippocampal degeneration. They observed that rats exposed to daily restraint stress, or given daily corticosterone (CORT) injections for 21 days, developed atrophy of the apical dendrites in hippocampal CA3 pyramidal cells. With severe stress, or extended daily administration of CORT for 12 weeks, the rats developed a permanent depletion in GRs, resulting from destruction of the host neurons themselves. According to the “Glucocorticoid Cascade Hypothesis”, periods of stress or excessive GC secretion result in the down-regulation of GRs in hippocampal neurons. A point is eventually reached where the decreased receptor number desensitizes hippocampal feedback inhibition of the HPA axis. A hypersecretion of GCs develops as a result of this disrupted feedback process, which leads to further receptor down-regulation and GC hypersecretion. Ultimately, there is permanent destruction of hippocampal neurons, at which point the cycle of destruction is irreversible (Sapolsky et al. 1986). A variety of investigations using stereological counting techniques in animals have contradicted selective aspects of the GC cascade hypothesis (Martin, 1990; Vollman-Honsdorf et al. 1997; West, 1993).

Many of the studies assessing GC impacts on brain functioning in animals have utilized long-term potentiation as an outcome variable. Long-term potentiation is the long-lasting strengthening of the response of a post-synaptic nerve cell to stimulation across the synapse that occurs with repeated stimulation, and is thought to be related to learning and long-term memory (Pease, 2002). In a seminal investigation, Diamond, Bennett, Fleshner, and Rose (1992) examined the relationship between the magnitude of hippocampal primed burst potentiation (a low threshold form of long-term potentiation) and the level of serum CORT using a sample of adrenalectomized (ADX) rats as the experimental group and adrenal-intact rats as the control group.

Findings revealed a positive correlation between low levels of serum CORT (i.e., 1-10 micrograms/dL) and hippocampal primed burst potentiation in the experimental group that reached a maximum at intermediate levels of CORT (i.e., 11-20 micrograms/dL). High levels of serum CORT were negatively correlated with primed burst potentiation, thus suggesting an inverted-U relationship between serum CORT and primed burst potentiation. The finding of an inverted-U-shaped relationship between serum CORT and long-term potentiation, or primed burst potentiation has been replicated by other investigators (Pavlidis, Watanabe, & McEwen, 1993; Roozendaal, 2000).

Another line of inquiry in the animal literature has examined GC effects on cognition utilizing spatial memory paradigms. Many forms of mazes (radial maze, T-maze, Morris water maze) have been used to measure the effects of adrenal steroids on animal cognition. Luine, Spencer, and McEwen (1993) investigated the effects of chronic ingestion of CORT (i.e., 8 weeks) on spatial memory performance and monoamine levels in rats. Twenty 10-month old rats each received one-week of training on a radial arm maze, followed by 20 trials (two trials/day, morning and afternoon for 2 weeks). After 20 trials on the maze, the rats were divided into two groups. The experimental group was administered 400 mg/ml of CORT dissolved in ethanol, while the control group received ethanol in water. Treatment continued for 8 weeks. Spatial memory was tested and evaluated on an 8-arm maze with a pellet of cat food serving as reinforcement.

Findings revealed that the overall performance of the CORT treated rats was unaltered; however, the performance of some of the CORT treated rats was impaired relative to the control group. The authors conclude that ingestion of CORT for 8 weeks may impair spatial memory performance in some CORT-treated rats. Other

investigations have illustrated similar negative effects of CORT on spatial memory in rats (Dachir, Kadar, Robinzon, & Levy, 1993; Issa et al., 1990).

In a similar vein, the direct effects of GCs on associative learning paradigms, as defined by various aspects of conditioning behaviours, have also been previously examined. Passive avoidance learning, acquisition of immobility response, and other associative learning paradigms consist of having an animal learn the association between two stimuli (Lupien & McEwen, 1997).

Kovacs, Telegdy, and Lissak (1976) reported that low doses of CORT facilitated extinction of an avoidance response, while high doses of CORT delayed the rate of extinction of the conditioned response. This biphasic modulatory effect of GCs has also been replicated using passive avoidance protocols. In chicks, passive avoidance learning tasks take advantage of the spontaneous tendency of one-day-old chicks to peck at small salient objects in their field of view. Normally, chicks presented with a small bead dipped in a bitter tasting liquid will initially peck at the bead and display an aversive reaction. They will subsequently avoid a similar, but dry bead for long periods after the initial presentation. However, if chicks are trained with less bitter tasting objects, or with diluted concentrations of the aversant (i.e., bitter tasting liquid), avoidance and hence memory decays in a matter of minutes or hours following training (Cordero & Sandi, 1998).

Sandi and Rose (1994) used the characteristics of this protocol to determine whether CORT administration would improve the long-term formation of passive avoidance learning in chicks. Their results revealed that intra-cerebral injections of CORT (1 microgram), either 15 min pre-training, or up to 1-hr post-training resulted in a significantly higher avoidance level in chicks tested at 24-hrs post-training, as compared to saline injected controls. The researchers concluded that the injections of CORT facilitated retention of the avoidance response beyond that of saline-injected controls.

The authors further found an inverted-U dose-response relationship between level of pre-training CORT and later retention. That is, the lowest and highest doses of CORT failed to influence avoidance learning, whereas the medium dose (i.e., 1 microgram) facilitated retention at 24-hrs post-training.

In a follow-up investigation, Sandi and Rose (1997) examined two further phenomena using chicks. First, they examined the effects of different concentrations (i.e., 10% and 100%) of the abovementioned aversant, on long-term memory, and plasma CORT levels. Second, they examined the effects of injecting different CORT doses (i.e., 0.1, 1, and 5 micrograms/chick) into an area of the hypothalamus called the intermediate medial hyperstriatum ventrale on memory acquisition and consolidation. Doses were administered in the post-training period (5 min), and the effects on the establishment of a long-term memory (as evaluated 24-hrs post-training) in chicks trained either with a 10% aversant, or a 100% aversant were evaluated.

Results revealed that only chicks trained on the strong aversant task (100%), a learning situation that results in a high percentage of chicks forming long-term memories, experienced an increased release of CORT because of training. Chicks trained in the weak aversant task (10%), which leads to retention of the avoidance response for only a few hours (i.e., <9 hrs), showed circulating CORT values comparable to untrained chicks. With regard to the second objective, results indicated a dose-dependent effect of CORT on long-term memory expression, as evaluated 24-hrs post-training. Intracerebral administration of 1 microgram of CORT facilitated long-term memory expression in the chicks trained with the weak task (10% aversant); however, a higher dose of 5 micrograms failed to produce this effect. Additional doses of 1 and 5 micrograms of CORT impaired long-term memory in the chicks trained with the strong task (100%) aversant (Sandi & Rose, 1997).

The authors draw several conclusions from these two investigations. First, a low central corticosteroid action appears detrimental to memory formation as training chicks in the 10% aversant condition did not produce any change in circulating CORT levels and resulted only in transient memory. Second, a moderate central corticosteroid action appears to facilitate the establishment of enduring memory. This conclusion was based on the observation that the chicks trained with the 100% aversant had increased circulating levels of CORT and also a long-term memory of the event and chicks trained with the 10% aversant and then given exogenous CORT also exhibited increased long-term memories for the event. Third, the authors conclude that excess CORT appears to be detrimental for the mechanisms of long-term memory formation since there was reduced retention in strongly aversant trained chicks (100%) additionally injected with 1 or 5 micrograms of CORT (Sandi & Rose, 1997).

The authors speculate that the contrasting memory abilities of chicks trained with the 10% or 100% aversant may be related to a differential manipulation of MR and GR receptors. Indeed, many of the results in the animal literature implicate involvement of MR and GR corticosteroid receptors in moderating the effects of corticosteroids on cognition, and particularly memory (Diamond et al. 1992; Kovacs, 1976; Lupien & McEwen, 1997; Sandi & Rose, 1997).

The first study to systematically manipulate MR and GR receptors, with the hope of further elucidating their relative contributions to memory acquisition and consolidation was conducted by Oitzl and DeKloet (1992). In this investigation, separate groups of adrenal intact rats were administered either MR or GR antagonists. Antagonist administration was given either before training the animal in the Morris water maze for the first time (pre-training/session 1), after training the animal in the Morris water maze for the first time (post-training/session 1), or before being measured on the Morris water maze for the second time (pre-session 2). In this manner, it was possible to measure

the effects of corticosteroid antagonists on the acquisition (i.e., pre-training/session 1) and consolidation (i.e., post-training/session 1) processes of memory. Finally, injecting the corticosteroid antagonists into another group of rats that had already learned (acquired and consolidated) the maze on a first occasion (pre-session 2), allowed the researchers to measure the effects of corticosteroid antagonists on the retrieval process.

The administration of the GR antagonist impaired the performance of the rats that were injected before and after their first session in the water maze. However, it did not affect the performance of rats that were injected before performing the maze for the second time (Oitzl & DeKloet, 1992). That is, when the animal was acquiring and/or consolidating the task, GR antagonist administration had a detrimental effect on their performance. However, once the animal had acquired and consolidated the task, GR antagonist administration no longer had an effect on performance. The authors conclude that GR receptors are involved in the process of memory consolidation.

On the other hand, the administration of the MR antagonist had no effect on the performance of the rats that were injected before and after their initial session in the water maze. Furthermore, it did not impair the performance of the rats that were injected before performing the maze on the second occasion. The authors were unable to elucidate a specific role of MR receptors in the process of memory formation based on these results. However, a subsequent investigation led the authors to suggest that MR receptors may be involved in the process of evaluating a situation and selecting an appropriate response (i.e., sensory integration) (DeKloet, Oitzl, & Joels, 1993).

Other investigators have replicated the results of this study. Sandi and Rose (1994) examined the effect of specific MR and GR antagonists on long-term retention of a passive avoidance-learning paradigm. They found that injection of the MR antagonist with CORT did not significantly alter retention of the avoidance response. The opposite was true when the GR antagonist was dovetailed with CORT administration (i.e.,

significant impairment of retention of the avoidance response). The authors concluded that MRs alter the chicks' reactivity to non-specific aspects of training (i.e., interpretation of environmental stimuli and selection of a behavioural response). Meanwhile, GRs appear to be involved in memory consolidation.

Recently, Conrad and collaborators investigated the effect of MR and GR agonists administered at three points in time (120 min prior to learning (i.e., Trial 1), immediately after Trial 1, or 120 min after Trial 1) on adrenalectomized (ADX) rats' performance on the Y-maze (Conrad, Lupien, Thanasoulis, & McEwen, 1997). Their design comprised four groups, including two groups of ADX rats administered an MR or GR agonist, an adrenal intact SHAM group administered a sesame vehicle, and an ADX group administered a sesame vehicle. The Y-maze is a two-trial recognition memory test that taps into the innate tendency of rats to explore new (i.e., never before encountered) environments.

Results revealed that the ADX rats treated with the MR agonist performed as well as the SHAM-treated rats with regard to spatial recognition memory. However, the ADX rats treated with the GR agonist performed as poorly as the ADX rats treated with the sesame vehicle. However, both experimental groups explored the Y-maze more than controls (ADX and SHAM) over the course of the entire experiment (prior to trial 1, immediately after trial 1, 120 min after trial 1) (Conrad, Lupien, Thanasoulis, & McEwen, 1997).

The authors suggest that the findings indicate a discrepancy in the proficient use of exploratory behaviour by the two experimental groups. Whereas, the rats treated with the MR agonist used inspective behaviour to acquire and/or consolidate spatial information, the increase in exploratory behaviour of the rats administered the GR agonist did not produce improved spatial recognition memory (recall that these are ADX rats, and hence there was no MR occupancy at the time of GR agonist administration).

Conclusions from animal investigations

Several tentative conclusions can be drawn about the effects of acute administration of GCs on cognition based upon the animal literature. First, there appears to be a preponderance of evidence implicating a dose-dependent relationship between level of serum corticosteroid and electrophysiological, and cognitive (i.e., spatial paradigms, passive-avoidance protocols) measures of brain function. This relationship most likely resembles an inverted-U shape with long-term potentiation and cognitive performance at their best with moderate exogenous levels of GCs. Second, the relationship between GC exposure and cognition appears to be dependent on the relative activation of the MRs and GRs. While MRs appear important for arousal and orientation to the environment, GRs appear more central to the process of memory consolidation. Third, the facilitational action of GRs appears dependent on the occupation of MRs. That is, when MRs are completely unoccupied, activation of GRs will not facilitate memory consolidation. Conversely, when both receptors are highly occupied, GRs have an inhibitory action on memory consolidation. Fourth, administration of selective MR or GR agonists or antagonists appears to be the definitive manner in which to study their relative contributions to various cognitive processes.

The remainder of this paper will focus upon the investigations that have examined the effects of GCs on human cognition. In contrast to the investigations using animals, the majority of these studies have utilized cognitive and neuropsychological tests as their primary outcome measures. Furthermore, the vast majority, have examined cognitive functioning in the context of acute supraphysiological doses of exogenous GCs. To date, there is a paucity of information regarding the long-term (i.e., one to two year) effects of therapeutic doses of exogenous GCs on cognitive functioning (Belanoff, Gross, Yager, & Schatzberg, 2001; Lupien & McEwen, 1997; Lupien & LePage, 2001; DeKloet, et al. 1999).

Investigations in Human Populations

Endogenous Glucocorticoids

A variety of studies have examined neuropsychological functioning in patients exposed, for various reasons (i.e., Cushing's Syndrome, Post-Traumatic Stress Disorder), to chronically elevated levels of endogenous GCs. Evidence has suggested that the effects of elevated endogenous GCs on neuropsychological functioning may be somewhat different from that of exogenous GC administration (Lupien et al., 2002a; Schmidt et al., 1999; Young, Sahakian, Robbins, & Cowen, 1999). A primary reason for this discrepancy may be the differential binding of MRs and GRs by endogenous versus exogenous GCs. CORT and cortisol bind preferentially to MRs, while synthetic GCs such as dexamethasone and prednisone have much higher affinities for GRs (Plihal, Krug, Pietrowsky, Fehm, & Born, 1996; Schmidt et al. 1999). Other reasons include differences in the time course and level of hypercortisolemia, and the presence or absence of related biochemical changes (i.e., alterations in levels of corticotropin releasing factor and ACTH) (Keller-Wood & Dallman, 1984). However, it appears reasonable to suggest that different individuals exposed to similar substances (i.e., cortisol and synthetic cortisol like substances) via somewhat different pathophysiological mechanisms, may display some similar cognitive characteristics. Therefore, a review of some of the germane literature with regard to one of the well-researched states of elevated endogenous hypercortisolemia (i.e., Cushing's Syndrome) will be provided.

Cushing's Syndrome

Cushing's Syndrome is an endocrine disorder characterized by an overproduction of steroid hormones, mainly cortisol, from the adrenal cortex (Martignoni et al., 1992). The syndrome is divided into an ACTH-dependent and an ACTH-independent subtype. The former comprises the condition resulting from pituitary ACTH overproduction, termed Cushing's disease. The latter is comprised of conditions

involving adrenal tumours (adenoma or carcinoma), or states in which excessive treatment with GCs has resulted in Cushing's Syndrome (Belanoff et al., 2001; Starkman et al., 1992).

Martignoni et al. (1992) examined neuropsychological functioning in 24 untreated patients diagnosed with Cushing's disease, all of whom presented with the condition for at least 1 year, compared to healthy controls. The investigators state that patients identified as having affective disturbances, psychosis, and confusional states were excluded; however, they do not report on measures utilized for determining exclusion. Patients were administered a standard neuropsychological battery that included tests of attention, memory, language, and visual-spatial abilities.

Findings indicated significant group differences on the Logical Memory and Visual Reproduction subtests of the WMS (both short and long delayed recall), and Digit Span backwards. In all cases, the performance of the patients with Cushing's disease was impaired relative to the control group.

Starkman, Gebarski, Berent, and Schteingart (1992) examined the relationship between hippocampal formation volume, memory dysfunction, and cortisol levels in 12 patients with Cushing's syndrome. They found that patients with Cushing's syndrome exhibited impaired performance relative to normal controls on both immediate and delayed (i.e., 30 minutes) verbal recall on the Logical Memory subtest of the (WMS). Interestingly, the researchers found a significant positive correlation between hippocampal formation volume and scores on tests of verbal learning and memory. Significant limitations to this study were the inclusion of subjects with both subtypes of the syndrome (i.e., sample comprised both ACTH-dependent and independent individuals) and the relatively small sample size.

More recently, Starkman, Giordani, Berent, Schork, and Schteingart (2001) examined neuropsychological functioning in 48 patients with untreated Cushing's

disease, relative to 38 healthy controls. Neuropsychological measures included several subtests of the WAIS-R, and the Mental Control, Visual Memory Span, Logical memory, Paired Associate Learning and Visual Reproduction subtests of the WMS. The subtests from the WMS were grouped into a composite memory score.

Patients with Cushing's disease performed significantly worse than controls on all three neuropsychological domains (i.e., WAIS-R Verbal and Performance IQ, and the WMS Memory composite). Post-hoc analyses revealed that the performance of the group with Cushing's disease was significantly lower than that of controls on four of the five verbal subtests of the WAIS-R (Comprehension, Vocabulary, Similarities, and Arithmetic). However, the only WAIS-R Performance subtest that differentiated the groups was Block Design, with the patients with Cushing's disease scoring significantly lower than controls. Patients with Cushing's disease performed significantly worse than controls on both measures of verbal memory from the WMS (i.e., Logical Memory and Paired Associate Learning), for both immediate and delayed recall trials. There were no significant differences between the groups on any of the other WMS subtests.

Starkman, Giordani, Gebarski, and Scheingart (2003) investigated whether the increase in the hippocampal formation volume of patients with Cushing's disease treated with a drug that lowered cortisol concentrations to normal levels would be associated with improvements in neurocognition. Neuropsychological testing included tests of verbal cognition, learning, and memory. After partialling out age, education, duration of illness, and time since surgical treatment, greater improvement in word list-learning was associated with a greater increase in hippocampal formation volume.

In a similar vein, Hook and colleagues sought to better understand whether the negative effects of cortisol on cognition in patients with Cushing's disease can be reversed and, if so, how long after successful treatment this recovery might begin. Participants included 72 patients with Cushing's disease, ranging in age from 18 to 72

years, tested at 3-5 months, 6-12 months, and 13-18 months, after successful surgical treatment. At all assessment periods cortisol samples were collected, and patients were administered a neuropsychological battery comprised of tests of verbal list-learning, verbal fluency, attention, and personality. In order to better examine the effects of age on the independent variables the sample was divided into “younger” and “older” subgroups. Participants in the younger subgroup ranged in age from 18-39 years, while those in the older subgroup ranged from 40-72 years (Hook et al., 2007).

Findings revealed a specific pattern of recovery post-surgery with significant recovery of verbal memory and fluency, but not brief attention. With regard to the question of age, participants in the younger subgroup exhibited a tendency to rebound more quickly on select cognitive tests post-surgery (verbal list-learning) relative to participants in the older subgroup. Finally, the improvement in verbal recall was associated with the increase in hippocampal formation volume one year after treatment (Hook et al., 2007).

Conclusions

Overall, the findings with regard to neuropsychological functioning in untreated Cushing’s syndrome have suggested that individuals exhibit impairments on tests of declarative memory. Additionally, there is some evidence of impairments on tests measuring aspects of executive functioning; however, these findings have not been as consistent. Modest evidence suggests that there may be a reduction of hippocampal formation volume in long-standing untreated Cushing’s syndrome that is associated with impairments in verbal learning and memory. An improvement in verbal memory and verbal fluency has been demonstrated after treatment of Cushing’s disease. The improvement in verbal memory has been associated with the increase in hippocampal formation volume after the treatment of Cushing’s disease. The rate of recovery may be faster for younger (18-40) versus older (45-70) patients with Cushing’s disease.

Normal Aging

Several studies have explored basal cortisol changes as a function of advancing age, with equivocal results. Cross-sectional studies have generally reported that basal cortisol levels do not change across the age-span in healthy subjects (Carvalhoes-Neto, Ramos, Vieira, & Kater, 2002; Waltman, Blackman, Chrousos, Riemann, & Harman, 1991). However, the results of within-subjects designs contradict these findings. For example, Deuschle et al. (1997) examined the diurnal and pulsatile features of the HPA system in 11 healthy females and 22 healthy males ranging in age from 25-85. All subjects underwent 24-hr blood sampling with 30-min sampling intervals. However, from 18.00 to 24.00 hrs, blood was sampled every 10 minutes for analysis of pulsatile features of HPA activity.

Results indicated a significant age-associated increase in mean plasma cortisol concentrations. Although there was no age-cortisol correlation during daytime, there was a strong impact of cortisol plasma levels in the evening (Deuschle et al., 1997). The researchers conclude that their results provide evidence for increased basal activity and flattened diurnal amplitude of the HPA system in the elderly.

Lupien et al. (1996) examined cortisol levels and neuropsychological performance in a group of 51 healthy elderly subjects (ages 60-90) over a 3 to 6 year period. Once per year, basal cortisol levels were examined using hourly sampling over a 24-hr period. Three cortisol measures were computed for each subject. These included the 24-hour averaged level (24-hr avg.), the cortisol slope, and the last 24-hour (last) measurement. The investigators performed a literature review when deciding what plasma cortisol level would constitute hypersecretion in aging, arriving at the value of 12.5 micrograms/ml/hr. Applying these three endocrine measures to their sample, they discovered the presence of three subtypes of elderly. The first group termed the Positive Slope Elevated Group, or PSE, demonstrated a positive cortisol slope and

elevated levels of both 24-hr avg. and last measures. This group comprised an estimated 23.5% of the population. The second and largest group termed Positive Slope Moderate, or PSM, comprised individuals with a positive cortisol slope, but below criteria (i.e., 12.5 mcg/ml/hr) levels of both 24-hr avg. and last measures. This group comprised an estimated 56.8% of the population. Finally, the third group termed Negative Slope, or NS, demonstrated both a negative cortisol slope and below criteria levels of 24-hr avg. and last measures. This group comprised an estimated 19.6% of the population.

Interestingly, the researchers were able to externally validate their typology using a battery that included experimental neuropsychological measures in the domains of memory (both immediate and delayed recall), attention (selective and divided), and language (verbal fluency and figural naming) (Lupien et al., 1996). The individuals in the PSE group exhibited impaired performance on selective attention and declarative memory tasks relative to individuals in the PSM and NS groups. The individuals in the PSM group demonstrated normal memory but deficits in vigilance relative to the other two groups. Finally, individuals in the NS group exhibited performance comparable to young healthy controls on all of the neuropsychological measures.

Lupien and colleagues have subsequently replicated their findings with regard to memory functioning in these three groups. Furthermore, they were able to show that the total hippocampal volume of the PSE group was significantly reduced by 14% relative to the other two groups (i.e., PSM and NS) (Lupien et al., 1998).

Seeman, McEwen, Singer, Albert, and Rowe (1997) used data from a community-based longitudinal study of older men and women, aged 70-79 years, to test the hypothesis that exposure to increasing levels of cortisol is associated with declines in memory. Neuropsychological measures included WMS Logical Memory (immediate and delayed recall) and the Boston Naming Test. Results indicated an association between greater cortisol excretion and poorer baseline memory performance in women.

Furthermore, women who exhibited increases in cortisol excretion over a 2.5- year follow-up period were more likely to show declines in memory performance. No such findings were produced for the men in their sample.

More recently, MacLulich et al. (2005) examined the hypothesis that higher plasma cortisol levels and altered sensitivity to GCs are associated with worse cognition and greater brain atrophy using a sample of healthy elderly males between 65 and 70 years of age. All subjects had plasma cortisol measured at 09:00 and 14:30 hrs of the same day. Furthermore, sensitivity to dexamethasone was assessed with a low dose dexamethasone suppression test during which 0.25 mg of dexamethasone was taken at 23:00 hrs and blood was drawn at 09:00 hrs the following morning. Cognitive testing included: Raven's Progressive Matrices (number correct in 20 minutes), WMS- Logical Memory (immediate and delayed recall) and Visual Reproduction, RAVLT, Controlled Oral Word Association Test and the National Adult Reading Test. Finally, all subjects underwent brain imaging via magnetic resonance imaging. Data reduction for cognitive test scores using principal components analysis was performed. The first unrotated component accounted for 51% of the variance in cognitive function, and was labelled the General Cognitive Factor.

Cortisol levels at 09:00 hrs correlated negatively and significantly with the general cognitive factor and Logical Memory 24-hr delayed. There was no significant correlation between hippocampal volume and cortisol level; however, the authors suggest that their use of a cross-sectional design may have limited their ability to find such an effect. Interestingly, although the investigators did not find a consistent relationship between cortisol levels and brain volumes, they did find a significant relationship (i.e., negative correlation) between 14:30 hr cortisol levels and left temporal lobe volume. Others have reported similar left-side worse laterality findings with elevated cortisol (Hull, 2002; van der Beek, et al., 2004).

Following the evidence of an association between increasing plasma cortisol and greater impairments of declarative memory, Li et al. (2006) explored the association between salivary cortisol and cognitive changes in cognitively intact older (mean age was 63 years) people in a 3-year longitudinal study. Cortisol samples were collected at home at 08:00, 15:00, and 23:00 hrs 2-3 days prior to the administration of neuropsychological tests annually for 3 years. Cognitive measures included tests of global cognition (Mini Mental State Exam), verbal memory (WMS-III Logical Memory), visual memory (delayed object recall), attention and concentration (Stroop test, TMTA and TMTB), and language (Boston Naming Test).

Findings revealed a significant association between cortisol levels at all three sampling points and poorer performance on tasks of declarative memory and executive functioning. Of the 46 participants who completed the entire 3-year study, higher initial cortisol concentration at 23:00 hrs predicted a decline in performance on the delayed recall component of the WMS-III logical memory subtest. Importantly, the study extended the findings of Lupien et al. (1998) in demonstrating that the subgroup of subjects with increasing cortisol concentrations over time (positive cortisol slope) consistently had the poorest verbal recall scores at the beginning, middle, and end of the study. Finally, analyses revealed a significant association between higher mean cortisol levels and poorer performance on the TMTB and the Stroop test. The authors suggest this finding is indicative of an influence of cortisol on structures in the prefrontal cortex.

In accordance with the evidence of a high concentration of corticosteroid receptors in the prefrontal cortex, McCormick, Lewis, Somley and Kahan (2007) examined the association between salivary cortisol levels and performance on the Wisconsin Card Sorting Test (WCST). Their sample included 120 undergraduate students between the ages of 17 and 22. Each participant was tested individually within

18:00 and 22:15 hrs, and saliva samples were collected before and after the completion of cognitive testing.

Results suggested a positive association between the first (arrival) sample of cortisol and perseverative errors on the WCST for women and a negative association between these values for men. The authors state that, for women, the finding is in accordance with the literature that reports a negative association between cortisol levels and working memory (Young, Sahakian, Robbins, & Cowen, 1999), while for men it is consistent with prior research that demonstrates a U-shaped relationship between cortisol levels and working memory (Lupien, Gillin, & Hauger, 1999). It should be noted that the mean arrival cortisol level for men in their sample was less than the value for women.

Conclusions

Based on the abovementioned studies, it is important to consider various methods of measurement when quantifying cortisol due to the temporal variability of this hormone. Second, an increase in the basal concentration of cortisol with aging may not be a universal phenomenon; rather, there may be subtypes of elderly individuals. Third, there is some evidence for impaired declarative memory and some aspects of attention in those individuals exposed to chronic endogenous hypercortisolemia (e.g., PSE group). Fourth, modest evidence suggests that there is an association between endogenous cortisol and executive functioning, and this relationship may vary by gender. Finally, there appears to be some evidence for a relationship between decreased hippocampal volume with chronic exposure to elevated endogenous cortisol.

Experimental Studies in Healthy Human Subjects

The effects of exogenous GCs on cognitive functioning in healthy individuals have also been examined. Wolkowitz et al. (1990) investigated the memory performance of 11 medically healthy, medication and caffeine free volunteers on a list-

learning task. All participants were screened for significant psychiatric conditions. Prednisone administration was carried out (80 mg daily for 5 days) in a double-blinded manner. Memory testing was conducted once during the initial 5-day placebo period, once after 4 days of prednisone administration, and once again 7 days after discontinuation of the prednisone. Findings indicated that prednisone was associated with a significantly higher rate of errors of commission (i.e., incorrectly identifying distractors as target words) than was placebo during the test of recognition memory. There were no significant effects of prednisone on measures of attention, or free recall. The first author has replicated these findings in a subsequent investigation (Wolkowitz, 1994).

Newcomer, Craft, Hershey, Askins and Bardgett (1994) examined the effects of 4-day administration of dexamethasone treatment on cognitive functioning in healthy adults. Cognitive testing was performed at 16:00 hrs before, during, and after a 4-day period of double-blinded, placebo-controlled treatment with dexamethasone. Subjects were administered dexamethasone at 23:00 hrs for four consecutive days (0.5, 1, 1, 1 mg, respectively). Cognitive measures included the logical memory subtest from the Wechsler Memory Scale-Revised (WMS-R), a serial addition task during which participants were asked to calculate the sum of a series of presented numbers, and the Benton Judgement of Line Orientation Test, a task in which participants are shown a line and must select the line it most closely matches in orientation from a presented array.

Results indicated significantly lower logical memory recall scores for the experimental group as compared to matched controls, but only after the fourth day of treatment with dexamethasone (Newcomer et al., 1994). The effect was apparent on both immediate and long delayed recall. While the performance of the control group on logical memory recall improved over the four treatment days (practice effect) that of the experimental group declined. There were no significant group differences on any of the

other cognitive measures. The finding that the experimental group made errors of omission but not commission on the paragraph recall task is in direct contrast to the Wolkowitz et al. (1990) investigation. The authors suggest that the discrepancy may be explained by the use of two different memory measures and the younger sample of participants in their study. Alternatively, the use of two different synthetic GCs may account for this discrepancy. The selective impairment of immediate and delayed recall on prose memory tasks has been replicated by other investigators (Brunner, et al., 2005; DeQuiervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Newcomer et al., 1999).

DeKloet (1993) points out that the rendering of statements regarding the effects of exogenous GCs on cognitive functioning in humans has been hampered by the methodological limitations of many of the studies thus far conducted. He points out that in the animal literature there has been an attempt to conduct investigations that allow for the differential manipulation of steroid receptors through use of agonists, antagonists, or hormone replacement protocols. This type of design has thus far been lacking in the human literature. Furthermore, few studies in the human literature have considered the circadian variation in endogenous cortisol levels when examining the effects of exogenous doses of GCs on cognition.

A recent pair of investigations by Lupien and colleagues (Lupien et al., 2002a, 2002b), were conducted to address some of these relevant issues. In the first study, (Lupien et al., 2002a) the experimenters used a hormone replacement procedure in a double-blinded placebo controlled protocol. They pharmacologically decreased cortisol levels by administration of metyrapone (a potent inhibitor of cortisol synthesis), and then, in the second study, restored baseline cortisol levels by subsequent hydrocortisone replacement therapy. Memory function, using a 12-word list presented over three trials, was assessed after each pharmacological manipulation. Both immediate and delayed (i.e., 20 min) recall was measured. Four different lists of words were used to rule out

practice effects. Treatment with metyrapone significantly impaired delayed recall in the experimental group relative to the placebo group, suggesting that metyrapone administration had a negative impact on the retrieval component of memory.

In the second investigation (Lupien et al., 2002b), researchers utilized the natural circadian fluctuation of cortisol, and tested the effect of a bolus injection of 35 mg of hydrocortisone on memory. Hydrocortisone was administered in the late afternoon, a time thought to coincide with a very low level of endogenous cortisol circulation. The dependent variable utilized was an incidental encoding task that required shallow and deep levels of processing. For the shallow encoding condition, subjects were asked to answer if the word presented to them contained the letter "T". These words were presented once and subjects had to answer "yes" or "no" using a keypad. Deep encoding required the subject to decide if the words presented to them contained more than one homonym. During recognition testing, 30 word stems were presented randomly to subjects. Each word stem comprised the first three letters of a word and the participant was required to indicate whether the presented word stem was part of a word previously presented or not.

Although there were no significant group differences on the word stem recognition task, there was a significant main effect of depth of processing. Shallowly encoded words consistently lead to lower recognition performances, when compared to deeply encoded words. Perhaps more notable was the finding that the treatment group responded significantly faster for all correct trials when compared to the placebo group (Lupien et al., 2002b).

Taken together, the results of these studies demonstrate that GCs can modulate human memory functioning, possibly via differential activation of MRs and GRs. The administration of metyrapone in the first investigation (Lupien et al., 2002a) likely resulted in a decreased production of cortisol, reduced MR occupancy with relatively

little GR occupancy, and, hence, deficient delayed memory. With regard to the second investigation, hydrocortisone injection in the afternoon (circadian trough, and a time when only MRs would have been occupied by the endogenous cortisol) may have led to partial activation of GRs. This may have resulted in increased cognitive efficiency in the group receiving hydrocortisone, relative to placebo (Lupien et al., 2002b).

Although there are several investigations highlighting the effects of exogenous GC administration on memory, other cognitive domains such as executive functioning have been implicated with less consistency. Executive functions have generally been operationalized as higher order control processes that integrate cognitive abilities, and that are primarily attributed to the frontal lobes (Baddeley & Della Sala, 1996). Specifically, they are thought to involve elements of response inhibition, self-regulation, planning, problem solving, cognitive set-shifting, and working memory (Reitan & Wolfson, 1994; Stuss & Benson, 1986). Working memory involves the process of holding information in storage temporarily, while simultaneously working on other cognitive tasks (Miyake et al., 2000). A good example would be trying to remember a string of digits, wherein one must keep the previously presented digits in mind while trying to encode new digits. Executive functions subsume a number of different cognitive operations and the term “executive functions” has been used interchangeably in the literature with such terms as “executive processes”, “higher-order abilities” and “complex attention” (Burgess, 1997). The term “complex attention” will be used to make reference to executive functions in the remainder of this paper. This is because the majority of the research presented here did not use measures of problem solving or concept formation, skills traditionally measured in studies of executive functioning (Stuss & Benson, 1986).

Young et al. (1999) examined the effects of hydrocortisone administration on learning, memory, and executive functioning. Subjects included 20 healthy male

volunteers with no history of a medical or psychiatric disorder. Subjects were administered hydrocortisone (20 mg twice daily) for 10 days in a randomized, placebo controlled, within-subjects crossover design. Neuropsychological measures included selected subtests of the Cambridge Neuropsychological Test Automated Battery including spatial working memory, paired associates learning, pattern and spatial recognition and the Tower of London test. Chronic (i.e., 10 day) administration of hydrocortisone was associated with more errors on both the spatial working memory and paired associates subtests of the Cambridge Neuropsychological Test Automated Battery. The authors conclude that the pattern of deficits produced by hydrocortisone administration is more consistent with frontal than hippocampal deficits.

Lupien, Gillin, and Hauger (1999) examined the effects of various doses of hydrocortisone on tasks assessing working memory and declarative memory in four groups of 10 healthy young men. During infusion, subjects were administered an item-recognition working memory task, a paired-associate declarative memory task, and a continuous performance task used to control for steroid effects on vigilance. They found significant acute effects of the highest dose of hydrocortisone on working memory without any significant effect on declarative memory. The authors conclude that working memory may be more sensitive than declarative memory to acute increases in GC levels.

It makes intuitive sense that deficits of particular aspects of complex attention would result after exogenous GC administration. Most exogenous GCs (i.e., hydrocortisone, prednisone) bind with great affinity to GRs that are distributed widely throughout the brain, but preferentially in the prefrontal cortex. Indeed, further investigation is required to substantiate the abovementioned findings with regard to deficits of complex attention, and to explore the exact nature of these deficits (Belanoff et al., 2001; Brunner et al., 2005; Sapolsky, 2000).

Conclusions

Acute administration of GCs to healthy controls negatively impacts declarative memory. This has been demonstrated using both paragraph recall and verbal list-learning tasks. There is also modest evidence to suggest impairments in some aspects of executive functioning within young adult (i.e., between 30 and 45 years old) subjects exposed acutely to high doses of GCs. The majority of investigations have failed to consider the circadian fluctuation of cortisol when drawing conclusions about exogenous GC administration. Furthermore, few studies have used GC agonists or antagonists to evaluate GC effects on cognition.

Glucocorticoid Therapy

GCs are used therapeutically for their anti-inflammatory and immunosuppressive properties to treat various conditions such as rheumatoid arthritis, and various autoimmune diseases. Despite this fact, there are few investigations examining GC action in patient groups treated for various conditions. This is likely due to the many confounding factors that would undoubtedly accompany such a design. However, such investigations are required to address the impacts of GCs on cognition in people for whom it may be a daily concern. A review of the most relevant work in this area is provided.

Rome and Braceland (1952) evaluated over 100 patients who were being treated with ACTH, cortisone, hydrocortisone and related substances for various conditions. They noted the common occurrence of “thinking disturbances” in these patients. This observation was subsequently reiterated by other investigators (Hall, Popkin, Stickney, & Gardner, 1979).

More recently, Keenan et al. (1996) conducted a dose-controlled cross-sectional design comparing memory performance between prednisone treated, patients without central nervous system involvement and normal controls. All patients in the

experimental group had been taking between 5 and 40 mg of prednisone ($M=17$ mg/day) daily for at least one year. Individuals were screened for the presence of any major psychiatric disturbances, or any other conditions that may confound the interpretation of results. The experimental group was heterogeneous and comprised individuals with various rheumatological or neurological conditions such as scleroderma, myasthenia gravis, rheumatoid arthritis, and chronic autoimmune hepatitis. Medical controls were closely matched with the experimental group on diseases.

Primary neuropsychological tests included measures of declarative memory (i.e., WMS Logical Memory subtest, California Verbal Learning Test), and implicit memory (i.e., Wordstem Completion Priming Task). Other domains assessed were visual spatial abilities (Judgment of Line Orientation), verbal fluency (Controlled Oral Word Association), non-verbal intellectual capacity (Raven's Progressive Matrices), non-verbal memory (Spatial Recall) and attention (The Vigilance Test and Digit Span Forward). The two groups were also administered a test of reading ability, and a disability inventory questionnaire to rule out confounds of general intellectual ability and disease severity respectively.

The treatment group recalled fewer bits of information on the Long-Delay condition of WMS- Logical Memory subtest. Furthermore, a strong non-significant trend was noted, wherein the control group outperformed the treatment group, on long-delayed memory from the California Verbal Learning Test. A significant difference on the List Learning Discriminability Score, an index of recognition memory, was also evident that favoured the control group. There were no significant group differences on any other measures. Results of multiple regression analysis revealed that patient age accounted for a significant proportion of the variance in Logical Memory recall scores. More specifically, there was evidence of an age by duration interaction. Increasing age

was associated with greater memory impairment in those patients taking the drug for up to 3 years, but not for those taking the drug between 4 and 15 years.

The results, according to the authors, indicate a declarative memory impairment, which was exacerbated with increasing age in individuals receiving chronic, moderate doses of prednisone. A unique aspect of this investigation was the inclusion of an implicit memory task that showed no group differences (i.e., the treatment group performed as well as controls). This finding has been previously demonstrated (Kirschbaum et al., 1996; Lupien et al., 1994).

Brown et al. (2004) have recently replicated some of the findings of the Keenan et al. (1996) investigation using a similar patient population. Their sample included 17 patients with various rheumatic diseases between the ages of 18 and 65 who had all been receiving treatment with prednisone (5-30 mg/day, M=17 mg/day) for at least 6 months and healthy age and IQ matched controls. All participants were screened for the presence of any current or past psychiatric problems; however, the investigators did include some individuals in their study who had a current or past history of mood or anxiety disorder secondary to GC therapy (n=10). These persons were included in order to better reflect the general population of people taking GCs, at least some of who develop such conditions. Primary neuropsychological tests included the RAVLT, Stroop Color Word Test, TMTA and TMTB, and the National Adult Reading Test.

The treatment group performed significantly worse than the controls on the RAVLT (Total words learned and 20-minute delayed recall) and the Stroop Color Word Test. No significant differences were found on any other measures.

In a subsequent investigation, Brown et al. (2007) conducted a 4-year follow-up study of corticosteroid-dependent patients and controls who all received mood, cognitive, and in two cases, structural magnetic resonance imaging (MRI) assessments at baseline (Brown et al., 2003; Brown et al., 2004). In total, seven prednisone treated patients and six controls agreed to reassessment with psychiatric symptom and

neurocognitive measures that included tests of verbal memory (RAVLT- total and delayed recall), and attention (Stroop test). Findings indicated that cognition was relatively stable over time in both groups. At the baseline assessment, the prednisone treated patients had poorer performance on the RAVLT- total words recalled, and the control group continued to outperform them at the follow-up assessment (i.e., the performance of the prednisone treated group remained stable with regard to this score). Although a trend toward worse performance on the Stroop test was evident, for the prednisone treated group, it was not statistically significant. The authors concluded that long-term prednisone therapy is associated with initial changes in memory that appear to stabilize over time.

In a slightly different vein Monastero and colleagues investigated the prevalence of cognitive impairment in patients with Behcet's disease without overt neurological involvement (Monastero et al., 2004). Behcet's disease is a chronic multi-system inflammatory disorder of unknown etiology. Their sample included 26 patients with Behcet's disease and a healthy control group all of whom underwent a comprehensive neuropsychological assessment. Of relevance to the present investigation, their sample of patients with Behcet's disease was divided into an impaired and an unimpaired group. Patients in the impaired group performed below the fifth percentile compared to age and education corrected norms on tests from at least two cognitive domains.

A comparison of the impaired and unimpaired groups revealed a statistically significant difference with regard to mean prednisone dose. Patients in the impaired group were maintained on an average dose of 11.9 mg/day, while those in the unimpaired group were maintained on an average dose of 2.8 mg/day (Monastero et al., 2004).

Conclusions

There is some evidence to suggest that prolonged moderate to high-dose therapy with GCs may have an adverse impact on declarative memory. This impact may vary as a function of age and duration of treatment, with older individuals treated for between one and three years being more sensitive to the adverse cognitive impacts of GCs. There is also modest evidence to suggest that doses in the lower end of the moderate range can have an adverse effect on cognition. There is a need for studies that not only extend the findings of those abovementioned with regard to memory, but also examine executive functions more closely using different patient populations, and different doses of GCs administered therapeutically (Brown et al., 2004; Dorn & Cerrone, 2000). As it stands, the findings with regard to declarative memory deficits after therapeutic treatment with GCs have been validated primarily in patients with Systemic Lupus Erythematosus (Denburg, Carbotte, & Denburg, 1994; Harrison & Ravdin, 2002).

General Conclusions

End-stage renal disease is a problem that is increasing worldwide. The first treatment choice for these patients is dialysis, either HD or PD. However, both these treatments are associated with a variety of complications (i.e., access infections, increased cardiovascular risk, and uremia). The preferred method of treatment for these patients is renal transplantation; however, access to viable organs and a shortage of living organ donors continue to be obstacles. There is extensive evidence demonstrating improved quality of life after transplantation compared to dialysis. Transplanted patients must comply with a wide array of post-transplant immunosuppressive agents. There is only modest evidence to suggest that these agents may have an impact on cognitive functioning, and this remains an avenue for future inquiry. Corticosteroids, and more specifically GCs, have traditionally been a vital part of the post-transplantation regimen, regardless of the organ transplanted. Although

there is currently the potential to manage some patients without steroids post-transplantation, particularly post-renal transplantation, epidemiological investigations indicate that steroids continue to be a staple for the majority of solid organ transplant recipients. Overall, the neurocognitive sequelae of end-stage renal disease, transplantation, and post-transplant immunosuppression require further investigation.

There is a wide body of literature addressing the impacts of GCs on cognitive functioning; however, the vast majority of these investigations have focused on states of excessive hypercortisolemia with regard to declarative memory. Furthermore, although the impact of acute, moderate to high doses of exogenous GCs on memory has been adequately documented, very little is known about the long-term ramifications (i.e., greater than one year) of exogenous, low dose, GC administration.

III. RATIONALE AND OBJECTIVES OF THE CURRENT INVESTIGATION

Rationale For the Present Investigation

There remain a need for investigations examining the long-term (i.e., greater than one year) impact of low dose exogenous GCs on cognitive functioning. Clinical populations for whom this situation may be directly relevant include those with certain rheumatic conditions and patients who are post solid organ transplantation. There appear to be only a couple of investigations in the literature thus far that have attempted to examine this phenomenon, and both have utilized heterogeneous samples of patients with various rheumatic and neurological conditions (Brown et al., 2004; Keenan et al., 1996). Furthermore, both investigations examined the impact of moderate to high doses of exogenous GCs (i.e., 16-20 mg/day) on cognitive functioning. Although this would certainly seem appropriate given the clinical populations utilized, it may not be applicable to recipients of solid organ transplants, the majority of whom receive chronic low doses of exogenous GCs (i.e., 2 to 10 mg/day prednisone). Theoretically, it is possible that even low doses of exogenous GCs delivered chronically may impair certain elements of cognitive functioning and the effects may be more deleterious in some older individuals (60-80 years old). There appears to be modest support for this hypothesis in the human literature utilizing samples of healthy individuals and geriatric patients (Keenan et al., 1996; Lupien et al., 1996; MacLulich et al., 2005; Newcomer et al., 1994).

The purpose of the present cross-sectional investigation was to examine cognitive functioning with regard to chronic low dose GC therapy using a sample of renal transplant recipients. The chronic steroid treatment group (CS group) included individuals who had been receiving low dose prednisone chronically for at least six months at the time of the study. The steroid avoidance group (SA group) consisted of renal transplant recipients in steroid avoidance protocols. Although some of these

individuals may have received high dose GCs 2-3 days after transplantation to prevent acute rejection, they had been steroid free for at least six months at the time of the study.

These two groups were compared with regard to their performance on a series of neuropsychological measures, with the primary cognitive domains of interest being declarative memory and complex attention. The majority of the domains were represented by composite category averages consisting of combined scores on different tests related to the same functional domain (e.g., the domain of attention may have consisted of scores on the TMTA and the PASAT).

The investigation was carried out to further elucidate the impact of chronic GCs administered therapeutically, and to aid in the medical management of renal transplant recipients, many of who deal with the ramifications of chronic exogenous GC therapy.

Primary Objectives

The effect of prednisone on declarative memory

To replicate the findings of previous investigators (i.e., Brown et al., 2004; Keenan et al., 1996) regarding the adverse effects of exogenous GC administration on declarative memory.

The effect of prednisone on complex attention

To further elucidate the effects of exogenous GC administration on particular aspects of complex attention (i.e., inhibition/disinhibition, working memory, set-shifting).

The impact of patient age, prednisone duration and dose on declarative memory

To examine the contribution that patient age, duration of GC administration, and drug dosage make to contributing variance in the declarative memory composite score for individuals in the CS group.

Primary Hypotheses

The effect of prednisone on declarative memory and complex attention

Hypothesis 1:

Based on the investigations conducted by Keenan et al. (1996) and Brown et al. (2004), it was expected that the performance of the CS group would be significantly worse than that of the SA group on the declarative memory composite domain. Specifically, it was predicted that the performance of the SA group would be significantly better than that of the CS group on the immediate and delayed recall components of the WMS-III Logical memory I and II subtests (Keenan et al., 1996; Newcomer et al., 1994). It was further predicted that the SA group would outperform the CS group on the RAVLT- Total words trials 1-5, 20 minute delayed recall scores, and recognition discriminability (Brown et al., 2004; Keenan et al., 1996).

Hypothesis 2:

Based on the few investigations that have examined complex attention (i.e., Brown et al., 2004; Lupien, Gillin, & Hauger, 1999; Young et al., 1999), it was predicted that there would be significant group differences on this composite domain. The performance of the SA group would be significantly better than that of the CS group on measures assessing working memory, inhibition/disinhibition, and set-shifting. Specifically, it was predicted that the SA group would demonstrate significantly greater scores on the WAIS-III Letter-Number sequencing subtest, WAIS-III Digit Span backward, and WMS-III Spatial Span backward tests than the CS group. Moreover, members of this group were expected to demonstrate fewer errors and a faster time to completion on the final trial of the Stroop colour word test, and fewer total errors on the 1 and 2-back conditions of the N-back test. Finally, it was predicted that they would demonstrate a faster time to completion and fewer errors on the TMTB.

The impact of prednisone on simple attention and processing speed

Hypothesis 3

Based on the Keenan et al. (1996) investigation, participants in the SA group were not predicted to significantly outperform those in the CS group with regard to the simple attention or processing speed composite scores.

The impact of patient age, prednisone duration and dose on declarative memory

Hypothesis 4

Patient age and duration of steroid treatment, but not dosage, were expected to predict a significant amount of variance in the declarative memory composite score for participants in the CS group. Specifically, it was predicted that increasing age and longer treatment duration would be associated with greater memory impairment. GC dosage was not predicted to impact the declarative memory composite score because all patients within the CS group were known to be within a relatively narrow band of dosing (i.e., between 2 and 10 mg/daily).

IV. METHODOLOGY

Participants

Participants received renal transplants through the Harper University Hospital solid organ transplantation program between the years 2002 and 2007. Initially, subjects were recruited for their possible inclusion in the study by one of the transplant nurses and the student researcher. Participants completed informed consent procedures in accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines, Wayne State University Human Investigations Committee regulations and University of Windsor Research Ethics Board regulations. Participants in both CS and SA groups were at least six months post-renal transplantation. Participants in the CS group had been receiving chronic low dose (i.e., 2-10 mg/day) prednisone since transplantation, whereas subjects in the SA group had been rapidly weaned off prednisone within the first few days following transplantation (avoidance).

The primary nephrologist decided whether an individual would receive chronic steroid medication. Although the protocol for deciding when a patient will receive steroids post-transplant varies, at Harper University Hospital the decision was made prior to transplantation and was based, almost exclusively, on immunologic variables which do not always correlate well with disease severity. Whenever possible, participants in both groups were matched on other medications administered as part of the post-transplantation regimen, such as tacrolimus and mycophenolate mofetil. Due to literature documenting a negative association between plasma levels of cyclosporine and aspects of cognitive functioning, renal transplant recipients maintained on cyclosporine were excluded from the study (Griva et al., 2004).

Other inclusion criteria for participants in both CS and SA groups were as follows: chronological ages between 18 and 60 years inclusive, a current level of adequate renal function (as assessed by the Cockcroft-Gault modification equation)

(participants were excluded if they demonstrated <30% functioning based on this equation, or if they obtained serum creatinine values of greater than 2.0 during their two most recent clinic visits), and English as their primary language, or at least fluency in written and spoken English. Values of renal function could not be obtained on the same day of neuropsychological testing for all participants. To provide a reliable estimate of renal function, the GFR values (as estimated from the Cockcroft-Gault equation) from the two most recent clinic visits were averaged.

Exclusionary criteria targeting confounds to the interpretation of results included uncorrected visual impairment (participants were told to bring reading glasses if they wore them), color blindness, uncorrected hearing loss, transplantation prior to 2002, documented intellectual disability, pregnancy or treatment with high-dose estrogens, cushing's syndrome, uncontrolled diabetes mellitus (excluded if hemoglobin A1C>14% for the average of their two most recent clinic visits), trauma, fever, or dehydration within the past two weeks, temporal lobe epilepsy, addison's disease, hypopituitarism or other endocrine diseases other than diabetes, HIV nephropathy, documented delirium during the 6 months prior to the study, current alcohol or drug abuse, treatment with cyclosporine, major psychiatric illness (based on documentation of an Axis I disorder on chart review, or a T-score of greater than 70 on the Global Severity Index of the Brief Symptom Inventory (BSI)). With regard to psychiatric history, if a patient exhibited a global severity index T-score between 63 and 70 on the BSI, they were administered a list of additional questions pertaining to symptoms of psychological disturbance. Testing was discontinued if the given patient endorsed a certain number of symptoms suggestive of an active psychological condition. It should be noted that these questions were asked even when a given patient obtained a GSI T-score of 70 or above (i.e., in the case of automatic discontinuation). Most of the other information was gathered through a review of medical charts and via interviews with the participants conducted prior to

testing. Whenever possible, participants were tested on the day of a regularly scheduled clinic appointment; otherwise, they came in for testing on a separate occasion.

Moreover, an attempt was made to test all participants during the same time of day, preferably in the afternoon, to better address the effect of GC therapy on cognition. This was done in accordance with the abovementioned literature that has demonstrated a consistent temporal variation in endogenous cortisol, with the trough occurring during the afternoon in humans (Lupien et al., 2002b; Newcomer et al., 1994).

Of the approximately 370 available cases in the renal transplant database at Harper University Hospital, 101 (26.5%) were excluded because patients had an age greater than 60. An additional 100 (26.3%) cases were discarded because patients were transplanted prior to 2002. Fifteen patients (4%) were excluded based on information from their records indicating the presence of an active psychiatric disturbance treated with medication. Approximately eighteen participants (5%) were excluded due to the presence of other disorders, outlined in the exclusionary criteria including lupus, seizures treated with medication, cancer of the brain, blindness, documented evidence of an intellectual disability, and recent motor vehicle accidents with documented evidence of head injuries. Twenty-five participants (6.5%) were excluded because they had serum creatinine levels greater than 2.0 during their two most recent clinic visits. Forty-two participants (11%) were excluded because they were on cyclosporine. Eleven patients (2.9%) were excluded because their Hemoglobin A1C values suggested uncontrolled diabetes. Approximately ten participants (2.6%) were excluded because they failed to show up for their appointments, refused to participate in the study outright, moved from the city, or were put back on dialysis. Approximately three patients (0.8%) were excluded on the basis of scores below cutoffs on the screening criteria. Finally, one person in the CS group was excluded on statistical

grounds and will be described further in the results section. The final sample contained thirty-nine participants, 17 in the CS group and 22 in the SA group.

Procedure

Once potential participants were recruited, the student researcher examined their medical records to determine their suitability for inclusion in the study. Participants were tested by the student researcher or his research assistant in a testing room within the Harper University Hospital renal transplantation clinic facilities. Whenever possible, the testing was dovetailed with their regular clinic appointment to avoid a separate trip to the clinic. Prior to testing, a short interview was conducted to gather relevant information not available in medical charts such as handedness, primary language, and years of education. Having participants identify the colours on one card of the Stroop Test assessed the presence of adequate colour recognition. To test auditory acuity, the examiner stood behind the participant and read a sentence aloud, that was repeated back by the participant. A formal test of English fluency was not administered; however, this information was gathered through the chart review and a discussion with the patient. Testing commenced with the administration of the screening measures. The student researcher or his research assistant scored these measures immediately to further determine participant suitability. If a potential participant was determined unsuitable at this point, they were paid ten dollars (half the total remuneration) and the reason for their exclusion was explained. If the results of the screening measures were within parameters, the rest of the testing was completed, and participants were paid twenty dollars.

The consent form explained that participants could go to the University of Windsor Ethics website to access the overall results of the study. The consent form is included in the Appendix B. Moreover, each participant was given a brief one-page summary of his/her performance on testing at the time of his/her next clinic appointment.

The feedback form was co-signed by the transplant psychologist. Where results of the study for a given individual revealed either a clinically significant cognitive deficit (i.e., an age-adjusted T-score greater than 1.5 standard deviations below the mean on a composite of memory, or a composite of complex attention), or evidence of a possible psychiatric condition (as denoted by a GSI T-score of greater than 70, or a T-score of between 63 and 70 with additional endorsement of screening questions suggestive of a possible psychological condition), the appropriate transplant nephrologist was contacted and made aware of this by the student researcher under the supervision and guidance of the transplant psychologist. These additional questions are included in Appendix C. An appropriate referral was made for the participant as needed at the time of his/her next regular clinic visit. As such, participants were made aware that their individual study results could be divulged to their primary transplant nephrologist.

Materials

The measures to be administered were sorted into the composite categories of declarative memory, complex attention, simple attention, and processing speed. A detailed description of all the tests utilized is presented in Table 2. The standard psychometric properties for the published tests are presented in Appendix D. The sources of the psychometric information are presented in Appendix E. Other tests administered as part of the screening process included: the BSI (Derogatis & Melisaratos, 1983), a questionnaire used to screen for psychiatric disturbance, the Wide Range Achievement Test- 3rd Edition (WRAT-3) reading Subtest (Wilkinson, 1993) used to estimate the pre-morbid level of general intellectual functioning, and, where required, the CAGE4, a four item measure frequently used to screen for alcohol abuse. Table 3 details the specific test scores comprising each composite category.

Although many of the cognitive measures utilized were related in some way to more than one of the abovementioned composite categories, each test/subtest was

included within the one composite category that appeared most appropriately related to the task demands of the particular test. Moreover, there was some evidence from prior research to sort the tests in such a manner (Jassal, Devins, Chan, Bozanovic, & Rourke, 2006). The composite categories were chosen on the basis of the literature review that revealed the sensitivity of these areas of cognitive functioning to the effects of steroids (Brown et al., 2004; Keenan et al., 2004; Newcomer et al., 1994). Similarly, the specific tests within the domains were chosen on the basis of the literature review that indicated their sensitivity to the effects of steroid exposure. For example, Keenan and colleagues demonstrated that moderate to high dose prednisone exposure caused decreased performance on the Logical Memory subtest of the Wechsler Memory Scale. Similarly, Brown and colleagues demonstrated decreased performance on the Stroop Colour Word test after moderate doses of prednisone exposure (Brown et al., 2004; Keenan et al., 1996).

V. FINDINGS

The formation of composite category scores

Because there was no normative base for all the measures in the battery, raw scores from each test were converted to z-scores based on the performance of all the participants in the study. The z-scores were averaged to form the required composite category scores. Z-scores were used for all statistical analyses. Where required, z-scores were adjusted so that, for all tests, positive z-scores denote better performances, while negative z-scores denote worse performances.

Description of statistical analysis and rubric for interpretation of strength of association

For the purpose of group-wise comparisons with regard to the cognitive dependant variable scores, variables were considered to be normally distributed, if the skewness and kurtosis values were between (-1.0 to +1.0) and if the result of the Shapiro-Wilk's test was not significant. Due to the fact that oppositely skewed variables can significantly impact the t-test with small sample sizes, boxplots and histograms were examined to ensure that, variables were skewed in the same direction, or were skewed in the opposite direction to a minimal extent.

Correlations were interpreted with regard to strength according to the criteria set forth by Cohen that dictates the following interpretations: weak (+/- .10 to +/- .29); moderate (+/- .30 to +/- .49); and strong (+/- .50 to +/- 1.0) (Cohen, 1988). All statistical analyses were conducted using SPSS version 14.0 for windows (SPSS Inc., Chicago, IL, USA).

Descriptive information by group on demographic, medical, and neuropsychological variables

Descriptive information for the relevant demographic and medical variables for participants in each of the two post-transplant groups is presented in Table 4 and illustrates that the two groups were relatively equivalent in terms of these variables.

Participants in the CS group were maintained on an average of 4.4 mg of prednisone (2.5 - 7.5 mg) for an average of 25.7 months (6 - 47.2 months). Wherever possible, age-adjusted scaled scores and age-adjusted t-scores were computed for neuropsychological test scores and this information is presented in Table 5. The specific published norms that were used to calculate the various age-adjusted scaled scores and t-scores are presented in Table 6. As can be seen from Table 5, based on age-adjusted normative data, participants in both study groups performed in the low-average to average range across tests. On an absolute basis, participants in the CS group outperformed participants in the SA group on the majority of tests.

Figure 1 depicts the average z-scores from each of the four composite domains for the CS and SA groups. Table 8 displays the average z-scores on each of the tests used to form the cognitive composite domains for the CS and SA groups. As noted in Table 5, for scores relative to external normative groups, the z-scores in Table 8 also reveal the better performance of the CS group relative to the SA group on the majority of measures.

Group comparisons on continuous demographic and medical variables

Either independent samples t-tests, or Mann Whitney-U tests were used to compare the two groups on the following continuous demographic and medical variables: duration of dialysis prior to transplant, GFR, mean mycophenolate mofetil dose, mean tacrolimus dose, systolic blood pressure, diastolic blood pressure, months since transplant, WRAT-3 reading score, BSI (GSI) score, age, and years of education. A Bonferroni-Holm's correction was applied to group-wise comparisons to control for the inflated Type I error rate associated with multiple comparisons. Given the small sample size in the present study and the chance of potentially excluding clinically meaningful data with too stringent a correction for multiple comparisons, the Bonferroni-Holm's technique was used instead of the Bonferroni technique, which is more conservative. A

series of Spearman's correlations were calculated to examine the relationship between the various continuous medical and demographic variables and the four cognitive composite domain scores. A Larzelere-Mulaik correction was applied to reduce the inflated Type I error rate associated with multiple correlations. The Larzelere-Mulaik procedure is an extension of the Holm's procedure used for controlling the Type I error rate associated with conducting multiple correlations. Where a particular continuous demographic or medical variable differed significantly between the groups and was significantly associated ($p < .05$) with one or more of the cognitive domain composite scores, that variable was treated as a covariate in an analysis of covariance (ANCOVA) for the cognitive composite domain in question. Where no covariates were identified, the cognitive composite domain scores were compared using a series of one-tailed independent sample t-tests, for normally distributed variables, or Mann-Whitney U-tests for non-normally distributed variables. Analyses were assessed at the $p < .05$ (*one-tailed*) level of significance.

Due to violations of normality, a series of Mann-Whitney U tests were conducted to examine group differences with regard to dialysis duration prior to transplant, dose of mycophenolate mofetil, dose of tacrolimus, and the WRAT-3 reading score. Group-wise comparisons for the rest of the continuous medical and demographic variables were assessed via independent samples t-tests. Results of these analyses are presented in Table 4 and suggest that, after correcting for multiple comparisons, the only variable that differed significantly between the groups was mean dose of mycophenolate mofetil per day, $U = 85$, $p = .00$. An examination of Table 4 indicates that participants in the SA group were maintained on a significantly higher dose of this drug than participants in the CS group. The other demographic and medical variables did not differ significantly between the two groups. However, before controlling for multiple comparisons, the group difference with regard to years of education was also statistically significant.

An examination of the scatterplots between the various continuous demographic and medical variables and the four cognitive composite scores revealed a non-linear relationship between age and the simple attention composite score. All the other relationships appeared to be linear. The results of a series of Spearman's correlations between the various continuous demographic and medical variables and the four cognitive composite z-scores for the entire sample are presented in Table 7. After correcting for multiple correlations, WRAT-3 reading was positively correlated with the complex attention composite score, $r_s(39) = .55, p = .00$, and duration of dialysis prior to transplant was negatively correlated with the processing speed composite score, $r_s(39) = -.57, p = .00$. There were no significant associations between any of the other continuous demographic or medical variables and the cognitive composite scores. Although not statistically significant after controlling for multiple correlations, the following continuous medical or demographic variables demonstrated moderate to strong positive associations with at least half of the cognitive composite scores: WRAT-3 reading, months since transplant and years of education. This suggests the hypothesis that overall cognitive efficiency post-transplantation appears to be associated with higher reading levels, greater education and a longer time since transplant. Similarly, although not statistically significant after controlling for multiple correlations, duration of dialysis prior to transplant exhibited moderately negative associations with the majority of cognitive composite scores suggesting the hypothesis that a longer bout of dialysis prior to transplant is associated with decreased cognitive efficiency post-transplantation. To further examine the non-linear relationship between age and simple attention, four roughly equivalent age categories were created and the non-linear coefficient of correlation was calculated, $\eta = .14$. The squared coefficient was found to be non-significant, $\eta^2 = .02, p > .05$.

Due to the fact that none of the continuous medical or demographic variables correlated significantly with the cognitive composite scores and differed significantly between the two groups, the majority were not included as covariates in primary comparisons of the SA and CS groups with regard to cognitive functioning. However, before adjusting for multiple comparisons, the group difference with regard to years of education was statistically significant. Moreover, this variable exhibited a moderate correlation with the complex attention composite score, $r_s(39) = .36, p = .02$. Therefore, this variable was included as a covariate when comparing the two groups with regard to the complex attention composite score.

Group Comparisons on categorical demographic and medical variables

A series of chi-square tests were conducted to examine the distribution of the categorical demographic and medical variables between the two groups. The variables included gender, handedness, proportion of African Americans, proportion of European Americans, proportion with hypertension, proportion receiving cadaveric transplants, proportion who underwent HD prior to transplantation, and the number of people treated with beta blockers. Where the chi-square test was significant for a particular variable, a Kendall Tau correlation was conducted between the variable in question and the four cognitive composite domain scores. These analyses were conducted to identify categorical demographic and medical variables that would confound factors to the interpretation of the results.

Table 4 details the results of chi-square analyses conducted on the categorical demographic and medical variables. None of the chi-square tests reached statistical significance, suggesting that all the categorical demographic and medical variables were independent of group membership. For handedness and proportion of European Americans, Fisher's Exact Test was conducted because some cell sizes in the chi-square were less than five. The result of Fisher's Exact Test was in accordance with the

chi-square test for both of these variables and was non-significant. The results of these analyses suggested that the categorical medical and demographic variables would not serve as significant confounds to the interpretation of results.

Screening for outliers

Before comparing the two groups with regard to cognition, all the dependant variables were screened for outliers. Based on the outlier analysis, one person was excluded from the CS group as he/she appeared to be an outlier on several cognitive measures (at least six). A further inspection of this profile suggested that this person was maintained on a different formulation of the antimetabolite, mycophenolate mofetil. Although it was unlikely that this difference could account for his/her discrepant performance on several cognitive measures, it was clear that the inclusion of this case could confound the findings. It should be noted that the analyses described in the previous section with regard to the demographic and clinical variables were conducted after this case was excluded. For the remaining cases, those outliers that were greater than 1.5 standard deviations from the mean were modified by a procedure wherein the outlying scores were assigned a score one point higher or lower than the next most extreme score in the distribution. This technique has been recommended in situations where there are a small number of outliers (Pedhazur, 2002). Approximately 10 data points were modified in this manner.

Inspection of the distribution of the cognitive test scores

To compare the two groups on specific tests, a series of one-tailed independent sample t-tests, for normally distributed scores, or Mann-Whitney U-tests for non-normally distributed scores were conducted. Unless otherwise noted, a Bonferroni-Holm's correction was applied to these analyses to control for the inflated Type I error rate associated with multiple comparisons. Analyses were assessed at the $p < .05$ (one-tailed) level of significance.

The impact of prednisone on performance in the four cognitive domains

Table 8 details the results of one-tailed group-wise comparisons on three of the four cognitive composite domains. Due to violations of normality, scores on the processing speed domain were compared using a Mann-Whitney U test whereas the declarative memory and simple attention domain scores were compared using one-tailed independent samples t-tests. The one-tailed test reached statistical significance with regard to the domain of simple attention, $t(37) = 2.52, p = .02$ (*one-tailed*). However, an examination of Figure 1 revealed that the direction of the result was opposite to what was predicted (i.e., participants in the CS outperformed those in the SA). To further examine this result, an ANCOVA was conducted with months since transplant as a covariate. Months since transplant was chosen because of the moderate association it exhibited with the simple attention domain, $r_s(39) = .42, p = .01$ (Table 7). The data were screened with regard to violations of the assumptions of normality, linearity, homogeneity of variance and homogeneity of regression slopes. After controlling for months since transplant, there was no reliable group difference with regard to the simple attention composite score, $F(1, 36) = .94, p = .08, \text{partial eta-squared} = .10$. Group differences with regard to the processing speed and declarative memory composite scores were not significant.

To compare the two groups with regard to the complex attention composite score, an ANCOVA was conducted with years of education as the covariate. After controlling for years of education, there was no significant group difference on the complex attention composite domain, $F(1, 36) = .94, p = .34, \text{partial eta-squared} = .03$.

Comparisons of the various test scores comprising each cognitive composite domain are presented in Table 8. Due to violations of normality, slightly less than half of the test scores were compared using one-tailed Mann-Whitney U tests with Bonferroni-Holms corrections. The remainder were compared using one-tailed independent

samples t-tests. After correcting for multiple comparisons, there were no significant group differences with regard to any of the test scores. However, before correcting for multiple comparisons, scores with regard to TMTA (time), digit span backward, letter-number sequencing, and stroop colour-word (time) were significantly better for the CS group than the SA group. Likewise, before correcting for multiple comparisons, the recognition discriminability score was significantly better for the SA group than the CS group.

The impact of patient age, prednisone duration and dose on declarative memory

Statistical analyses with regard to the third goal were conducted on the CS group. Therefore, z-score composites for all the variables were re-calculated based on the mean of the CS group. A series of correlations were conducted between current kidney function as assessed by the GFR, systolic blood pressure, diastolic blood pressure, years of education, duration of dialysis, mean mycophenolate mofetil dose, mean tacrolimus dose, WRAT-3 reading score, months since transplant, and the declarative memory z-score composite. This was done to assess the possible impact of the continuous demographic and medical variables on declarative memory. Similarly, a series of Kendall's Tau correlations were conducted to examine the relationship between the categorical demographic and medical variables and the declarative memory composite score. Where the correlation was statistically significant, the variable in question was controlled for in a multiple regression analysis. Where these variables failed to significantly correlate with the declarative memory composite score a standard regression was conducted using age, prednisone duration, and prednisone dose as the independent variables.

Selection of appropriate predictors for regression analyses

To ascertain if the drug effect on the declarative memory z-score composite was influenced by patient age, dose or duration of steroid treatment, a sequential multiple regression was conducted. Before conducting the analysis, the data were screened for violations of assumptions of normality, linearity, homoscedasticity and independence of residuals. To control for their effect, the demographic and medical variables abovementioned that significantly ($p < .05$) correlated with the declarative memory z-score composite were entered in the first block of the sequential multiple regression. Following this, patient age, treatment duration and drug dosage was entered into the model. Where the medical, or demographic variables failed to correlate significantly with the declarative memory z-score composite, a standard multiple regression was conducted using patient age, duration of prednisone treatment, and prednisone dose as the independent variables. Again, the results of all individual analyses within the model were assessed at the $p < .05$ level of significance.

The results of correlations between GFR, systolic blood pressure, diastolic blood pressure, years of education, months since transplant, WRAT-3 reading, duration of dialysis prior to transplant, mean mycophenolate mofetil dose, mean tacrolimus dose and the declarative memory composite score for participants in the CS group are presented in Table 9. Although none of the correlations reached statistical significance, there was a trend towards significance in the positive direction for the relationship between months since transplant and declarative memory, $r_s(17) = .48, p = .05$, and in the negative direction for the relationship between dialysis duration prior to transplant and declarative memory, $r_s(17) = -.44, p = .07$. Table 10 presents the results of Kendall's Tau correlations between the categorical demographic and medical variables and the declarative memory composite score. None of these correlations reached

statistical significance suggesting that these variables would not have to be included in any regression analyses.

Due to the small sample size of the CS group ($n=17$), a decision was made to conduct a standard regression analysis with a minimum number of predictors. A series of correlations between mean prednisone dose, prednisone duration, patient age, and the declarative memory composite score were conducted to select appropriate predictors. An examination of the scatterplots between each of the independent variables and the declarative memory composite score revealed a non-linear relationship between prednisone dose and declarative memory. The other relationships appeared to be linear in nature and the results of these analyses indicated that prednisone duration was significantly associated with the declarative memory composite score, $r_s(17) = .49$, $p = .04$, whereas patient age was not, $r_s(17) = .25$, $p = .34$. The positive association between prednisone duration and the declarative memory composite score was unexpected. Therefore, a series of correlations between prednisone duration and the other continuous demographic and medical variables were conducted to examine the possibility of a moderating variable. After controlling for multiple comparisons, there was a strong positive relationship between months since transplant and prednisone duration, $r_s(17) = .94$, $p = .00$. The results of the other correlations did not reach statistical significance. The finding of a strong positive association between months since transplant and prednisone duration was not surprising as the majority of patients in the CS group (11/17) had been initiated on prednisone immediately post-transplantation. The other patients were initiated on prednisone a mean of 3.8 months post-transplantation. A partial correlation between prednisone duration and declarative memory, controlling for months since transplant, was not statistically significant, $r_{12.3}(17) = .22$, $p = .41$. Based on this analysis, prednisone duration was not included as an

independent variable in a regression analysis as the interpretation of results would be confounded by its strong correlation with months since transplant.

The scatterplot of the nonlinear relationship between prednisone dose and declarative memory for participants in the CS group is presented in Figure 2. It was evident that the one data point at 7.5 mg of prednisone was modifying the relationship between the variables (i.e., with that point removed the relationship between prednisone dose and memory appeared to be negative and linear as opposed to curvilinear). The clinical significance of this one data point was unclear; therefore, the data were analyzed with its inclusion and exclusion. The non-linear relationship between prednisone dose and declarative memory was calculated (with the inclusion of the influential data point) and found to be reasonably strong, $\eta = .648$. Likewise, the linear relationship (with the point excluded) between prednisone dose and declarative memory was significant, $r_s(16) = -.63, p < .05$, indicating an association between a higher dose of prednisone and a poorer memory score. To check for the possibility of a variable moderating the relationship between prednisone dose and declarative memory, a series of Spearman's correlations (with the exclusion of the influential data point) and a series of eta coefficients (with the inclusion of the point) were conducted. Table 11 presents the results of Spearman's correlations (with the exclusion of the influential data point) and the corresponding eta-squared values (with the inclusion of the point) for the relationships between prednisone dose and the other continuous medical and demographic variables. Although none of the correlations reached statistical significance after controlling for multiple correlations, there was a strong negative linear correlation between months since transplant and prednisone dose, $r_s(16) = -.62, p = .01$, indicating an association between a greater time since transplant and a lower dose of prednisone. These analyses indicated that the vast majority of the continuous medical

and demographic variables did not appear to be modifying the relationship between prednisone dose and declarative memory.

The results of these preliminary analyses suggested that the most appropriate predictor for regression was prednisone dose. Furthermore, based on the findings of a trend towards significance for the relationship between duration of dialysis prior to transplant and declarative memory, $r_s(17) = -.44$, $p = .07$, a decision was made to include this variable as an independent variable in a regression analysis. Due to the nonlinearity of the relationship between prednisone dose and declarative memory, two separate analyses were conducted.

The influence of dialysis duration prior to transplant on post-transplant declarative memory

An initial standard regression of the effect of dialysis duration prior to transplant on the declarative memory score was conducted to examine violations of linearity, homoscedasticity, normality, and to check for the presence of outliers. The normal probability plot was acceptable as was the scatterplot of the residuals. These plots are presented in Figure 3. The overall model was statistically significant, $F(1, 15) = 4.83$, $p = .04$, and suggested that duration of dialysis prior to transplant predicted almost 20% of the variance in the declarative memory score post-renal transplantation (*Adjusted R*² = .19). The regression table for the model is presented in Table 12. Specifically, the direction of the Spearman's correlation indicated a trend wherein greater duration of dialysis prior to transplantation was associated with poorer declarative memory post-transplantation, $r_s(17) = -.44$.

The influence of prednisone dose on post-transplant declarative memory

The relationship between prednisone dose and declarative memory was initially analyzed with the exclusion of the influential data point. Prednisone dose appeared to be categorical in its distribution with people either receiving 2.5 mg, or 5 mg of

prednisone. A separate variable was created that represented these two levels of the drug. It was clear from its strong correlation with prednisone dose, $r_s(16) = -.62, p = .01$, that months since transplant would have to be controlled. Initial screening for its inclusion as a covariate in an ANCOVA revealed its moderate degree of correlation with the declarative memory composite score, $r_s(16) = .49, p = .06$. Further screening demonstrated that months since transplant exhibited a linear relationship with the declarative memory score for participants receiving 2.5 and 5 mg of prednisone. A formal test for the violation of homogeneity of regression slopes was not significant, $F(1, 12) = .58, p = .46$, indicating that months since transplant exhibited a similar relationship with the declarative memory score for participants receiving both drug dosages. A univariate ANCOVA was conducted with prednisone dose as the independent variable, months since transplant as the covariate, and the declarative memory score as the dependent variable. After controlling for months since transplant the difference in the memory scores of patients receiving 2.5 versus 5 mg of prednisone was not statistically significant, $F(1, 13) = 4.60, p = .05$. However, it exhibited a strong trend towards significance. Specifically, an examination of the estimated marginal means suggested that participants receiving 5 mg of prednisone had relatively worse declarative memory scores ($M = -.31, SD = .22$) compared to participants receiving 2.5 mg of prednisone ($M = .61, SD = .34$). Overall, prednisone dose accounted for approximately 26% of the variance in the declarative memory composite score, (*partial-eta squared* = .26). On the contrary, after adjusting for dose of prednisone, months since transplant accounted for approximately 6% of the variance in the declarative memory composite score, (*partial-eta squared* = .59).

Overall, the results of this analysis suggested that prednisone dose accounted for a noteworthy portion of the variance in the declarative memory composite score after controlling for the effect of months since transplant. Moreover, patients receiving 5 mg

of prednisone appeared to have relatively poorer declarative memory scores compared to patients receiving 2.5 mg of prednisone after controlling for months since transplantation.

To ascertain the impact of the influential 7.5 mg data point, a test of non-linearity was conducted that was statistically significant indicating some mild degree of non-linearity in the model with this value included, $F(1, 14) = 4.92, p = .04$. The value of non-linear association was calculated, $\eta = .648$ and the squared coefficient was found to be statistically significant, indicating that prednisone dose predicted a significant amount of variance in the declarative memory composite score, $\eta^2 = .42, p < .05$. Due to the very small sample size, a polynomial regression was not conducted to ascertain the possible nature of the non-linear relationship; however, an examination of the scatterplot suggested the possibility of a quadratic relationship. The results from the non-linear model were interpreted with caution as the coefficient of non-linear association is significantly influenced by small cell sizes and in this case, the influential point represented a cell size of just one.

Exploratory analyses

Based on the statistical analyses carried out to address the first three goals, it was decided to conduct additional analyses to further explore the data. First, the analyses revealed a significant negative relationship between duration of dialysis prior to transplant and the post-transplant declarative memory composite score for participants in the CS group. A Spearman's correlation between these two variables for the SA group was not significant, $r_s(22) = -.39, p = .11$. Similarly, the relationship between months since transplant and declarative memory for participants in the SA group was not statistically significant, $r_s(22) = .20, p = .35$, but was in the positive direction. Finally, the relationship between WRAT-3 reading and declarative memory for participants in the SA group was strongly significant, $r_s(22) = .55, p = .01$.

Table 7 illustrates a moderate to strong relationship among WRAT-3 reading, months since transplant, and duration of dialysis prior to transplant with at least half of the cognitive composite domain scores for the entire sample. To further explore this finding, a composite score reflecting a measure of general cognitive efficiency was calculated by averaging the four major cognitive composite z-scores (i.e., declarative memory, simple attention, complex attention, and processing speed) for the entire sample ($N = 39$). A standard multiple regression was conducted with WRAT-3 reading, months since transplant, and duration of dialysis as independent variables and the global measure of cognitive efficiency as the dependant variable.

The overall model was statistically significant, $F(3, 35) = 11.52, p = .00$, and revealed that these three variables combined predicted almost 50% of the variance in the cognitive efficiency composite score, (*Adjusted* $R^2 = .45$). Specifically, dialysis duration prior to transplantation, ($\beta = .31, p = .02$), and WRAT-3 reading, ($\beta = .46, p = .00$), contributed a significant portion of the variance in the cognitive efficiency composite score, while the contribution of months since transplant was not statistically significant. Dialysis duration prior to transplant and WRAT-3 reading combined predicted just over 40% of the variance in the cognitive efficiency composite score ($R^2 = .41$).

The results of the statistical analyses pointed to the important relationship between specific medical and demographic variables and cognitive functioning in this relatively small sample of renal transplant recipients.

VI. DISCUSSION

The present investigation examined the effect of chronic low dose prednisone on neuropsychological functioning in renal transplant recipients. Specifically, post-renal transplant recipients enrolled in a SA or a CS protocol were compared with regard to their cognitive performances in the domains of declarative memory, simple attention, complex attention, and processing speed.

With regard to group-wise comparisons, based on the literature reviewed, it was predicted that participants in the SA group would significantly outperform participants in the CS group with regard to the domains of declarative memory and complex attention. No such differences were predicted for the domains of simple attention or processing speed. Contrary to the predictions, there were no reliable group differences on the domains of declarative memory or complex attention. Moreover, participants in the CS group significantly outperformed those in the SA group with regard to the domain of simple attention. However, this difference was not apparent after including months since transplant as a covariate. As predicted, there were no significant group differences with regard to the domain of processing speed.

With regard to group-wise differences on specific tests, after controlling for multiple comparisons, there were no reliable group differences on any test. Before controlling for multiple comparisons, participants in the CS group performed significantly better than those in the SA group on the following test scores: TMTA (time), letter-number sequencing, stroop colour-word (time), and digit span backward. Likewise, before controlling for multiple comparisons, participants in the SA group significantly outperformed those in the CS group with regard to recognition discriminability on a verbal list-learning test.

With regard to the first hypothesis regarding the effect of low-dose, chronic prednisone on declarative memory, the results of the present investigation were not

generally in accordance with that of the literature reviewed (Brown et al., 2004; Keenan et al., 1996; Newcomer et al., 1994). There were no significant group differences with regard to the declarative memory composite score, or on the specific test scores that comprised this composite score (RAVLT-Total words trials 1-5, 20 min delayed recall scores, and Logical memory I and II subtests). There are several differences between the current study and those abovementioned that likely account for the discrepant findings. First, the studies by Brown and colleagues and Keenan and colleagues examined declarative memory in relation to moderate to high doses of prednisone. In both of those studies participants were maintained on a mean dose of 17 mg of prednisone daily, compared to the current study in which participants were maintained on an average dose of 4.4 mg of prednisone daily. Second, Newcomer and colleagues used a different corticosteroid (dexamethasone), an exogenous corticosteroid with a potency 4-5 times that of prednisone and a longer duration of action (Longui, 2007). Finally, whereas the current investigation used a control group of individuals matched with regard to the primary disease (i.e., kidney disease), the study by Keenan and colleagues used a control group comprised of individuals with various, rheumatic diseases. It is possible that the heterogeneous nature of their sample may have contributed to their significant results. Similarly, the study by Brown and colleagues compared the cognitive performance of their steroid treated participants to that of healthy controls.

Interestingly, the current study revealed that, before correcting for multiple comparisons, the performance of the SA group with regard to the recognition discriminability score was significantly better than that of the CS group. This finding is in accordance with the study by Keenan et al. (1996) in which prednisone treated patients performed more poorly than controls on the recognition discriminability score from the California Verbal Learning Test. Unfortunately, due to the non-normal distribution of this

score in the current study, the finding could not be further examined by inclusion of a covariate. Moreover, it is important to note that this difference was not significant after controlling for multiple comparisons suggesting that it needs to be replicated with a larger sample to determine its legitimacy.

With regard to the predictions concerning the effect of low-dose, chronic prednisone on complex attention, the findings of the present investigation were not in accordance with the reviewed literature that suggested an adverse impact of moderate to high doses of exogenous GCs on aspects of complex attention such as working memory, conceptual set-shifting and inhibition (Brown et al., 2004; Lupien, Gillin, & Hauger, 1999; Young et al., 1999). There were several differences between the current study and the investigations reviewed that may account for the divergent results. First, two out of three of the studies reviewed used a different corticosteroid (i.e., hydrocortisone), and examined cognitive functioning over days of administration of this drug (in both studies hydrocortisone was administered for 10 days). Second, there were differences, from the present study, in the neuropsychological measures used to evaluate complex attention. Young and colleagues utilized subtests from the Cambridge Neuropsychological Test Automated Battery, while Lupien and colleagues used an experimental measure of working memory. Finally, both of these studies examined cognitive functioning in groups of young healthy males as opposed to a clinical sample. While the investigation of Brown and colleagues was similar to the current study in their use of a clinical population and prednisone therapy, they, like the others, examined cognitive functioning in relation to moderate to high doses of prednisone. Moreover, their control group consisted of healthy individuals as opposed to clinical controls.

With regard to the fourth hypothesis regarding group differences on the domains of simple attention and processing speed, as predicted, there were no significant group differences on the processing speed domain. Furthermore, there were no group-wise

differences on specific tests from this domain. In terms of the simple attention domain, contrary to our hypothesis, participants in the CS group appeared to outperform those in the SA group. However, this difference was not present after including months since transplant as a covariate.

Contrary to expectations, there were no reliable differences between the CS and SA groups with regard to the cognitive test scores. One possible explanation of this result concerns the effect of exogenous GCs on the HPA axis. Evidence from animal investigations suggests that the relative occupancy of MRs and GRs in the brain partly determines cognitive efficiency in rats. When the ratio of MR/GR occupancy is low (as in the case of low circulating GCs, or treatment with excessive exogenous GCs) cognitive functioning is hampered. Conversely, cognitive functioning is optimal when the MR/GR occupancy is high (as in the case of moderate doses of exogenous GCs) (Conrad et al., 1997; Oitzl & DeKloet, 1992; Sandi & Rose, 1997). Investigations with humans have subsequently reiterated the ability of GCs to modulate aspects of cognitive functioning (memory) and have lent indirect support to the mechanism of action being via the differential activation of MRs and GRs (Lupien et al., 2002a; Lupien et al., 2002b). In the context of the present investigation, a tentative hypothesis would be that a low dose of exogenous prednisone is not detrimental to cognitive functioning because it does not result in the necessary degree of activation of GR receptors to alter the ratio of MR/GR occupancy. This hypothesis likely oversimplifies the relationship being examined as the question of optimality in terms of levels of circulating GCs is influenced by several factors including genetics, actual stress exposure, and the time of day (Herbert et al., 2006).

A second viable and somewhat more tenable explanation for the finding of the lack of reliable group differences has to do with the influence of specific demographic and clinical variables on cognitive functioning in this study. In the present study, months

since transplant, years of education, and WRAT-3 reading all exhibited moderate positive correlations with at least half, and in some cases (i.e., WRAT-3 reading), all of the cognitive composite scores. Participants in the CS group exhibited relatively greater scores on all of these variables than participants in the SA group (i.e., greater time since transplant, more years of education, and higher reading scores). Therefore, it is possible that it was the marginal differences with regard to these demographic or clinical variables that led to the lack of reliable group differences with regard to the cognitive tests scores.

The second main goal of this investigation was to examine the relationship between age, prednisone duration, and prednisone dosage for participants in the CS group. In accordance with the reviewed literature, it was predicted that age and prednisone duration would account for a significant portion of the variance in the declarative memory score. Prednisone dose was not expected to significantly predict the declarative memory score in our sample because all the patients in the CS group were maintained within a relatively narrow band of dosing (i.e., 2.5 - 7.5 mg/day).

Contrary to the predictions, an initial examination of the data indicated that age was not significantly correlated with the declarative memory score for participants in the CS group. Furthermore, although prednisone duration was significantly correlated with the declarative memory score, it was also strongly correlated with months since transplant. It was not included as an independent variable in the regression analysis because the interpretation of the results of such a regression would be confounded by its strong relationship to months since transplant. The results of preliminary analyses suggested that dialysis duration prior to transplant, and prednisone dose would be the best independent variables for regression analyses.

A simple linear regression of dialysis duration prior to transplant on the declarative memory composite score for participants in the CS group was significant and

revealed that this variable accounted for almost 20% of the variance in the declarative memory composite score. After controlling for months since transplant, the memory difference between patients receiving 2.5 mg or 5 mg of prednisone was not statistically significant but exhibited a strong trend towards significance. Prednisone dose predicted approximately 26% of the variance in the declarative memory composite score. Patients maintained on 5 mg of prednisone exhibited relatively poorer memory scores relative to patients maintained on 2.5 mg. When an influential data point of 7.5 mg was included the model appeared to be non-linear. Under these conditions prednisone dose accounted for a significant portion of the variance in the declarative memory composite score.

The finding that age was not significantly associated with the declarative memory composite score for patients maintained on prednisone was unexpected based on the literature reviewed. Keenan et al., (1996) found that increasing age was significantly associated with poorer memory for patients receiving prednisone for less than 3 years. More generally, the failure in the present study to find any significant associations between age and any of the cognitive composite scores for the entire sample of post-transplant patients was quite surprising. Investigations examining groups of post-renal transplant recipients have demonstrated a significant association between increasing age and poorer neuropsychological performance, particularly in the domains of learning and memory, and attention, concentration and processing speed (Griva et al., 2006; Griva et al., 2004). One possible explanation of the discrepancy in the present findings from that of others is that the studies reviewed included older participants, while patients greater than 60 years of age were excluded in the current investigation. For example, Keenan and colleagues included patients between the ages of 55 and 73. Moreover, patients in their sample were exposed to a higher mean dose of prednisone. Another potential explanation of the failure to find an association between age and cognition may

be due to the small sample size of transplant recipients enrolled ($N= 39$) in the current study. By comparison, Griva and colleagues acquired a sample size of 117 post-renal transplant recipients (Griva et al., 2004).

In contrast to the expected findings, the results of the present investigation suggest that even low doses of prednisone predict a noteworthy proportion of variance in predicting declarative memory. Perhaps more importantly, even within such a narrow band of dosing (2.5 - 5 mg/daily) one can discern differences in relative memory efficiency. Patients receiving 2.5 mg of prednisone exhibited a score on the declarative memory composite of approximately 56-T, while those receiving 5 mg of the drug exhibited a score of roughly 47-T. There are only a few other investigations that have examined the effect of prednisone dose on declarative memory in post-renal transplant recipients (Bermond et al., 2005; Monastero et al., 2004). Bermond et al., (2005) demonstrated a negative effect of prednisone doses between 10 and 27 mg on the delayed recall of auditory-verbal information, while Monastero and colleagues demonstrated that patients receiving approximately 11 mg of prednisone daily were more impaired with regard to some domains of cognitive functioning than those receiving approximately 2 mg daily (unimpaired), although it was unclear on which specific cognitive domains the differences occurred. The findings presented in the current study suggest that even low doses of prednisone may have an adverse impact on at least some aspects of cognitive functioning (i.e., declarative memory) but require replication with larger sample sizes.

The significant association between duration of dialysis prior to transplantation and post-transplant neurocognition was also unexpected. There are only a few investigations in the transplantation literature that have examined this association. Griva et al. (2006) found a significant inverse association between improvement on a psychomotor task and time spent on dialysis. Gelb and colleagues failed to find any

significant associations between duration of dialysis and measures of neurocognition in their sample of post-renal transplant recipients (Gelb et al., 2007). While Gelb and colleagues examined renal transplant recipients who had received dialysis for a mean of approximately 2.6 years prior to transplant, patients in the current study had received dialysis for a mean of 4 years prior to transplant. Moreover, while the majority of patients in the current sample (SA, 64%; CS, 70%) were maintained on HD prior to transplant, it is unclear what the relative composition of dialysis modalities was in that study. Both of these factors may explain the divergent results of the two investigations. However, given the literature that demonstrates a significant adverse effect of HD on aspects of neurocognition (Pereira et al., 2007; Pliskin et al., 1996; Umans & Pliskin, 1998) and the finding that HD is also associated with an increased risk for cardiovascular disease, sub-clinical white matter disease, and anemia all of which have, by themselves, been associated with cognitive impairment, the finding of an association between greater dialysis duration prior to transplant and worse post-transplant cognitive efficiency is not entirely surprising. The findings of the present investigation suggest that further exploration of this relationship in post-renal transplant recipients is warranted.

Another finding from the current study that is of interest is the relationship of months since transplant to neurocognition. Gelb et al., (2007) failed to find any significant associations between time since transplant and measures of learning and memory, or attention, concentration and processing speed. By contrast, in the current investigation moderate correlations were found in the positive direction between months since transplant, and the composite domains of simple and complex attention for the entire sample. The discrepancy in the findings of the current study from those of Gelb and colleagues with regard to the domain of attention and concentration may be due to the differences in cognitive tests that were utilized. In comparison to their study, the current included auditory span tests and an experimental version of an auditory working

memory test to assess attention. More generally, the results of the current analysis, with regard to months since transplant were consistent with their findings and indicated that it did not predict a significant proportion of variance in general cognitive efficiency for the entire sample. Moreover, although at first blush time since transplant appeared to exhibit a moderately positive association with the declarative memory composite score for participants in the CS group, after controlling for its strong association with prednisone dose, it predicted only approximately 6% of the variance in the declarative memory score.

Clinical Implications

Treatment with low dose, chronic prednisone post-renal transplantation does not appear to exacerbate cognitive dysfunction beyond the level that can be attributed to renal-transplantation itself. In the current study, participants in the SA and CS protocols performed similarly with regard to the domains of declarative memory, simple attention, complex attention, and processing speed. In comparison to age-corrected normative data, participants in both groups performed in the low-average to average range across tests. This finding is in accordance with that of other investigations (Griva et al., 2004; Griva et al., 2006). This is undoubtedly positive news for recipients of renal transplantation, and solid organ transplantation in general, as many of these individuals are enrolled in steroid maintenance protocols.

The current study also revealed that participants maintained on 2.5 mg of prednisone post-transplantation exhibited relatively better memory scores compared to those maintained on 5 mg of the drug. A somewhat important implication of this finding is that if participants are enrolled in steroid maintenance protocols they should be maintained on the lowest possible dose of prednisone possible, as it is possible that higher doses, even within relatively low dose ranges, are associated with poorer memory performance. This finding also argues in favour of steroid tapering wherein the initial

post-transplant dose of prednisone is reduced to the lowest level that will continue to prevent graft rejection. The importance of this finding is attenuated by the fact that participants in the SA group failed to exhibit significantly better memory performances than those in the CS group. Furthermore, given the rather small sample size employed, there is a need for replication of this finding.

In the current study it was found that the duration of dialysis prior to transplant predicted a significant portion of the variance in post-transplant declarative memory. Moreover, exploratory analyses further revealed that it significantly predicted general cognitive efficiency, post-renal transplantation. Our findings imply that longer periods of dialysis, and specifically HD, prior to transplant are associated with poorer memory and cognitive efficiency post-transplantation. This finding reiterates the importance of exploring alternative regimens of dialysis and using pre-emptive protocols, where possible, so participants are transplanted directly without ever having to initiate dialysis. Finally, in the current study it was found that months since transplant was moderately associated with at least half of the cognitive composite scores for the group as a whole (i.e., simple attention and complex attention). Furthermore, although it did not contribute a significant portion of the variance in the declarative memory composite score after adjusting for prednisone dose, it did exhibit positive associations with declarative memory for both the CS and SA groups. The findings with regard to time since transplant point to the possibility that neurocognition post renal transplantation appears to improve with a greater time since transplant. Although this finding makes intuitive sense, the results presented here warrant further investigation of the relationship of this variable to post-transplant neurocognition.

Limitations

There were several significant limitations in the present study. Chief amongst these was the small sample size utilized that prevented the examination of more intricate

relationships between variables and also significantly reduced the power of the analyses that were conducted. As an example, for the regression of dialysis duration on the declarative memory composite score, the calculated power with a sample size of 17, an alpha level of .05, and an $R^2 = .193$ was approximately 48%. If we had wanted the power to be closer to 80% on an a priori basis, then the sample size of the CS group would have had to have been approximately $n = 35$, a substantially larger sample.

Another obvious limitation of the study is the lack of a group of healthy control participants to which the performance of the two clinical groups could be compared. The inclusion of such a group would have enabled finer conclusions to be drawn about the possible effect of low-dose chronic prednisone on particular tests relative to healthy controls. It would have also helped to assess the possible clinical significance of performances on tests for which no age-corrected normative data was available (e.g., the auditory version of the N-back test).

Although the current study employed relatively rigorous inclusionary and exclusionary criteria it was not possible to match participants in the SA and CS groups with regard to all of the clinical and demographic variables. This somewhat limited the internal validity of the study, as group differences in cognitive functioning may have been attributable to these confounding variables. Clearly, a more definitive manner to study the phenomena under observation would be through the use of a longitudinal design. Such a design would also enable one to draw more definitive conclusions about the effects of such variables as duration of dialysis, and time since transplant on cognitive functioning.

In the current study participants with a wide variety of problems were excluded including clinically significant psychological symptoms, evidence of uncontrolled diabetes, and those maintained on cyclosporine just to name a few. The rigorous exclusionary criteria likely limit the generalizability of our results to some extent as most

clinical populations of renal transplant recipients likely include some individuals in these categories.

Although the primary researcher was able to equate both post-renal transplant groups with regard to a variety of variables such as medications, age, and estimated level of current kidney function, it was not possible to include various markers of immunological status such as level of panel reactive antibodies at transplant because this information was unavailable. Furthermore, due to the cross-sectional nature of the investigation, there may have been group differences in terms of pre-transplant variables that the analyses were unable to address.

There are obvious merits to the examination of the effect of low dose steroids using cumulative dosing strategies wherein a patient's exposure to the drug over a long period of time is taken into consideration. Unfortunately, it was not possible to examine this phenomenon in the current study because the information was unavailable.

One of the secondary objectives in the current study was to attempt to test participants in the afternoon so we could more clearly explicate the effect of exogenous corticosteroid therapy on cognition. This was done in accordance with the literature that has demonstrated a consistent temporal variation in endogenous cortisol, with the trough occurring during the afternoon in humans (Lupien et al., 2002b; Newcomer et al., 1994). However, because the renal-transplant clinics were typically held in the morning it was no possible to meet this objective. All of the patients in the current investigation were tested in the morning.

Unfortunately it was not possible to examine the relationship between biochemical measures and cognitive functioning because the lab values could not always be collected on the day of testing. For this same reason, average values of GFR had to be averaged to obtain reliable estimates of kidney function.

Although the findings presented here suggest a relationship between dialysis duration prior to transplant and post-transplant declarative memory it was not possible to examine the contribution of dialysis compliance as a variable moderating this relationship. Furthermore, although patients in the CS group were maintained on prednisone, it was not possible to examine the contribution of medication compliance in an examination of reliable group differences between the CS and SA group.

Future Investigations

The limitations listed above suggest several possible avenues of research for future studies. First, in light of the low statistical power in the present investigation, it would certainly be worthwhile to replicate the current findings with a larger sample size. Given the difficulty in obtaining participants from this patient population this may be optimally achieved through a large multi-center investigation. It is also important that a control group of healthy, age-matched participants be included for comparative purposes. Second, a longitudinal investigation would be the most definitive manner in which to examine the effect of prednisone on cognition as participants could serve as their own controls. Moreover, this would enable one to more carefully examine the rate and trajectory of detrimental cognitive changes that occur as a result of chronic pre-transplant HD and more clearly delineate the rate and extent of the positive cognitive changes that appear to occur as a result of renal transplantation. Third, it may be interesting to replicate the current study with an older sample of renal transplant recipients. Given the evidence that at least some groups of elderly patients exhibit increased endogenous cortisol levels, they may be more sensitive, in terms of cognitive functioning, to even low levels of exogenous GCs (Lupien et al., 1996). Fourth, it would be worthwhile to include additional variables such as dialysis and medication adherence and markers of immunological status in future investigations examining similar

phenomena. Finally, future investigations should continue to consider the importance of the diurnal variation in endogenous cortisol when designing paradigms.

In conclusion, the findings presented here suggest that post-renal transplant recipients maintained on chronic, low-dose prednisone are not more cognitively compromised than those who are not. However, the possibility was raised that prednisone dose post-transplant does appear to have a relationship with memory functioning as patients maintained on relatively higher doses of the drug (i.e., 5 mg) exhibited relatively poorer memory performances than those maintained on lower doses (i.e., 2.5 mg). Moreover, the results suggest that further exploration into the nature of the relationship between chronic prednisone therapy and neurocognition in this patient population is warranted.

BIBLIOGRAPHY

- Adamczak, M., Zeier, M., Dikow, R., & Ritz, E. (2002). Kidney and hypertension. *Kidney International*, *61*(80), S62-S67.
- Angelucci, A. (2000). The glucocorticoid hormone: From pedestal to dust and back. *European Journal of Pharmacology*, *405*, 139-147.
- Atkins, R.C. (2005). The epidemiology of chronic kidney disease. *Kidney International*, *94*, S14-S18.
- Baddeley, A.D., & Della Sala, S. (1996). Working memory and executive control. *Philosophical Transactions of the Royal Society of London*, *351*, 1397-1404.
- Bayley, P.J., & Squire, L.R. (2003). The medial temporal lobe and declarative memory. *International Congress Series*, *1250*, 245-259.
- Belanoff, J.K., Gross, K., Yager, A., & Schatzberg, A.F. (2001). Corticosteroids and cognition. *Journal of Psychiatric Research*, *35*, 127-145.
- Benetoli, A., Pagnelli, A.R., Giordani, F., Lima, K.C.M., Filho, L.A.F., & Milani, H. (2004). Effect of tacrolimus (FK506) on ischemia-induced brain damage and memory dysfunction in rats. *Pharmacology, Biochemistry and Behaviour*, *77*, 607-615.
- Bermond, B., Surachno, S., Lok, A., Berge, I.J.M., Plasmans, B., Kox, C., Schuller, E., Schellekens, P.T.A., Hamel, R. (2005). Memory functions in prednisone-treated kidney transplant patients. *Clinical Transplantation*, *19*, 512-517.
- Bishop, M.C. (2001). Infections associated with dialysis and transplantation. *Current Opinion in Urology*, *11*, 67-73.
- Brown, E.S., Frol, A., Bobadilla, L., Nejtek, V.A., Perantie, D.C., & Dhillon, H. (2003). Effect of lamotrigine on mood and cognition in patients receiving chronic exogenous corticosteroids. *Psychosomatics*, *44*, 204-208.

- Brown, E.S., Woolston, D.J., Frol, A., Bobadilla, L., Khan, D.A., Hanczyc, M., et al. (2004). Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biological Psychiatry*, *55*, 538-545.
- Brown, E.S., Vera, E., Frol, A.B., Woolston, D.J., & Johnson, B. (2007). Effects of chronic prednisone therapy on mood and memory. *Journal of Affective Disorders*, *99*, 279-283.
- Brunner, R., Schaefer, D., Hess, K., Parzer, P., Resch, F., & Schwab, S. (2005). Effect of corticosteroids on short-term and long-term memory. *Neurology*, *64*(2), 335-337.
- Burgess, P.W. (1997). Theory and methodology in executive function research. In P. Rabbit (Ed.), *Methodology of frontal and executive function*. New York: Plenum Publishers.
- Burrows-Hudson, S. (2005). Chronic kidney disease: An overview, early and aggressive treatment is vital. *American Journal of Nursing*, *105*(2), 40-49.
- Cameron, J. (1997). Rheumatology and the kidney. In A. Davison, J.S. Cameron, J.P. Grunfeld, D.N.S. Kerr, E. Ritz, & C.G. Winearls (Eds.), *Oxford textbook of clinical nephrology*, 2nd Edition, (pp. 2709-2716). Oxford University Press.
- Carmori, M.L., & Mauer, M. (2003). Diabetes and nephropathy. *Current opinion in nephrology and hypertension*, *12*, 273-282.
- Carvalhoes-Neto, N., Ramos, L.R., Vieira, J.G., & Kater, C.E. (2002). Urinary free cortisol is similar in older and younger women. *Experimental Aging Research*, *28*(2), 163-168.
- Chadban, S., Briganti, E., & Kerr, P. (2003). Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *Journal of the American Society of Nephrology*, *14*, S131-S138.
- Christe, W. (1994). Neurological disorders in liver and kidney transplant recipients. *Transplantation Proceedings*, *26*(6), 3175-3176.

- Churchill, D.N., Bird, D.R., Taylor, D.W., Beecroft, M.L., Gorman, J., & Wallace, J.E. (1992). Effect of high-flux hemodialysis on quality of life and neuropsychological function in chronic hemodialysis patients. *American Journal of Nephrology*, *12*, 412-418.
- Cohen, J.A., & Raps, E.C. (1995). Critical neurologic illness in the immunocompromised patient. *Neurologic Critical Care*, *13*(3), 659-677.
- Cohen, J.W. (1988). *Statistical power analysis for the behavioral sciences*, 2nd Edition. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Conrad, C.D., Lupien, S.J., Thanasoulis, L.C., & McEwen, B.S. (1997). The effects of type I and type II corticosteroid receptor agonists on exploratory behaviour and spatial memory in the Y-maze. *Brain Research*, *759*, 76-83.
- Cordero, M.I., & Sandi, C. (1998). A role for brain glucocorticoid receptors in contextual fear conditioning: Dependence upon training intensity. *Brain Research*, *786*, 11-17.
- Coresh, J., Astor, B.C. & Greene, T. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *American Journal of Kidney Disease*, *41*, 1-12.
- Craven, J.L. (1991). Cyclosporine-associated organic mental disorders in liver transplant recipients. *Psychosomatics*, *32*(1), 94-101.
- Cunnard, R., & Kelly, C.J. (2003). Immune-mediated renal disease. *Journal of Allergy and Clinical Rheumatology*, *111*(2), S637-644.
- Dachir, S., Kadar, T., Robinson, B., & Levy, A. (1993). Cognitive deficits induced in young rats by long-term corticosterone administration. *Behavioural Neural Biology*, *60*, 103-109.
- Dahm, K.J., & Cooper, M.E. (2002). Hypertension and diabetes. *Current Opinion in Nephrology and Hypertension*, *11*, 221-228.

- Danovitch, G. (2005). *Handbook of kidney transplantation*. Philadelphia: Lipincott, Williams and Watkins.
- DeKloet, E.R., Oitzl, M.S., & Joels, M. (1993). Functional implications of brain corticosteroid receptor diversity. *Cell and Molecular Neurobiology*, *13*(4), 433-455.
- DeKloet, E.R., Oitzl, M.S., & Joels, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neuroscience*, *22*, 422-426.
- DeLeon, M.J., McRae, T., Rusinek, H., Convit, A., DeSanti, S. Tarshish, C., et al. (1997). Cortisol reduces hippocampal glucose metabolism in normal elderly, but not in Alzheimer's disease. *Journal of Clinical Endocrinology and Metabolism*, *82*, 3251-3259.
- Denburg, S.D., Carbotte, R.M., & Denburg, J.A. (1994). Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, *37*(9), 1311-1320.
- DeQuervain, D., Roozendaal, B., Nitsch, R.M., McGaugh, J.L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nature Neuroscience*, *3*(4), 313-314.
- Derogatis, L.R., & Melisaratos, N. (1983). The Brief Symptom Inventory: An introductory report. *Psychological Medicine*, *13*, 595-605.
- Deuschle, M., Gotthardt, U., Schweiger, U., Weber, B., Korner, A., Schmider, J., et al. (1997). With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. *Life Sciences*, *61*(22), 2239-2246.
- Diamond, D.M., Bennett, C.M., Fleshner, M., & Rose, G.M. (1992). Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus*, *2*(4), 421-430.

- DiMartini, A., Pajer, K., Trzepacz, P., Fung, J., Starzi, T., & Tringali, R. (1991). Psychiatric morbidity in liver transplant patients. *Transplantation Proceedings*, 23(5), 3179-3180.
- Dorn, L.D., & Cerrone, P. (2000). Cognitive function in patients with cushing's syndrome. *Clinical Nursing Research*, 9(4), 420-440.
- Eaton, D.C., & Pooler, J.P. *Vander's renal physiology, 6th Edition*. (2004). Lange Physiology Series. McGraw-Hill Publishing.
- El Nahas, A. M., & Bello, A.K. (2005). Chronic kidney disease: The global challenge. *The Lancet*, 365(9456), 331-340.
- Eustace, J.A., & Coresh, J. (2005). Chronic kidney disease: Definition and epidemiology. In B.J.G. Pereira, M.H. Sayegh & P. Blake (Eds.), *Chronic kidney disease, dialysis and transplantation* (pp. 1-20). Philadelphia, PA: Elsevier & Saunders.
- Fervenza, J. (2005). Hypertension as a cause and consequence of ESRD? *Current Opinion in Nephrology and Hypertension*, 17, 111-122.
- Fervenza, M. (2003). Pathophysiology of hypertension in end-stage renal disease. *American Journal of Hypertension*, 32, 110-122.
- Fiebiger, W., Mitterbauer, C., & Oberbauer, R. (2004). Health-related quality of life outcomes after kidney transplantation. *Health and Quality of life Outcomes*, 2(2), 1-6.
- Flack, J.M., Peters, R., Shafi, T., Alrefai, H., Nasser, S.A., & Crook, E. (2003). Prevention of hypertension and its complications: Theoretical basis and guidelines for treatment. *Journal of the American Society of Nephrology*, 14, S92-98.
- Ganesh, S.K., Hulbert-Shearon, T., Port, F.K., & Stack, A.G. (2003). Mortality differences by dialysis modality among incident ESRD patients with and without

- coronary artery disease. *Journal of the American Society of Nephrology*, 14, 415-424.
- Gelb, S., Shapiro, R.J., Hill, A., & Loken-Thornton, W. (2007). Cognitive outcome following kidney transplantation. *Nephrology, Dialysis, Transplantation*, (December), 1-7.
- Gilli, P., & DeBastiani, P. (1983). Cognitive function and regular dialysis treatment. *Clinical Nephrology*, 19(4), 188-192.
- Glasscock, R.J. (2004). The rising tide of end-stage renal disease: what can be done? *Clinical and Experimental Nephrology*, 8, 291-296.
- Gokal, R., & Mallick, N.P. (1999). Peritoneal dialysis. *The Lancet*, 353, 823-828.
- Gotch, F. A., & Sargent, J.A. (1985). A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney International*, 28, 526-534.
- Grimm, G., Stockenhuber, F., Schneiweiss, B., Madi, C., Zeitlhofer, J., & Schneider, B. (1990). Improvement of brain function in hemodialysis patients treated with erythropoetin. *Kidney International*, 38, 480-6.
- Griva, K., Hansraj, S., Thomson, D., Jayasena, D., Davenport, A., Harrison, M., et al. (2004). Neuropsychological performance after kidney transplantation: A comparison between transplant types and in relation to dialysis and normative data. *Nephrology, Dialysis, Transplantation*, 19, 1866-1874.
- Griva, K., Newman, S.P., Harrison, M.J., Hankins, M., Davenport, A., Hansraj, S., et al. (2003). Acute neuropsychological changes in hemodialysis and peritoneal dialysis patients. *Health Psychology*, 22(6), 570-578.
- Griva, K., Thompson, D., Jayasena, D., Davenport, A., Harrison, M., & Newman, S.P. (in press). Cognitive functioning pre- to post-kidney transplantation- a prospective study. *Nephrology, Dialysis, Transplantation*.

- Hagberg, B. (1974). A prospective study of patients in chronic hemodialysis: Predictive value of intelligence, cognitive deficit and ego defense structures in rehabilitation. *Journal of Psychosomatic Research, 18*, 151-160.
- Hall, R.C.W., Popkin, M.K, Stickney, S.K., & Gardner, E.R. (1979). Presentation of the steroid psychoses. *Journal of Nervous Mental Disorders, 167*(4), 229-236.
- Harrison, M.J., & Ravdin, L.D. (2002). Cognitive dysfunction in neuropsychiatric systemic lupus erythematosus. *Current Opinion in Rheumatology, 14*(5), 510-514.
- Hart, R.P. (1983). Chronic renal failure, dialysis, and neuropsychological function. *Journal of Clinical Neuropsychology, 5*(4), 301-312.
- Harvey, J.N. (2003). Trends in the prevalence of diabetic nephropathy in type I and type II diabetes. *Current Opinion in Nephrology and Hypertension, 12*, 317-322.
- Herbert, J., Goodyear, I.M., Grossman, A.B., Hastings, M.H., DeKloet, E.R., Lightman, S.L., et al. (2006). Do corticosteroids damage the brain? *Journal of Neuroendocrinology, 18*(6), 393-411.
- Himmelfarb, J. (2002). Success and challenge in dialysis therapy. *New England Journal of Medicine, 347*(25), 2068-2070.
- Hook, J.N., Giordani, B., Schteingart, D.E., Guire, K., Giles, J., Ryan, K., et al. (2007). Patterns of cognitive change over time and relationship to age following successful treatment of cushing's disease. *Journal of the International Neuropsychological Society, 13*, 21-29.
- Hricik, D.E. (2005). Steroid withdrawal for the (selected) masses. *American Journal of Transplantation, 5*, 639-640.
- Hull, A.M. (2002). Neuroimaging findings in post-traumatic stress disorder: A systematic review. *British Journal of Psychiatry, 181*, 102-110.

- Issa, A.M., Rowe, W., Gauthier, S., & Meaney, M.J. (1990). Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *Journal of Neuroscience, 10*, 3247-3254.
- Jackson, M., Warrington, E.K., Roe, C.J., & Baker, L.R.I. (1987). Cognitive function in hemodialysis patients. *Clinical Nephrology, 27*(1), 26-30.
- Jassal, S.V., Devins, G.M., Chan, C.T., Bozanovic, R., & Rourke, S. (2006). Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: A longitudinal pilot study. *Kidney International, 70*, 956-962.
- Jones, C.A. (2003). Hypertension and renal dysfunction: NHANES-III. *Journal of the American Society of Nephrology, 14*, S71-75.
- Kaufman, D.B., Shapiro, R., Lucey, M.R., Bustami, R.T., & Dyke, D.B. (2004). Immunosuppression: Practice and trends. *American Journal of Transplantation, 4*(9), 38-53.
- Keenan, P.A., Jacobson, M.W., Soleymani, R.M., Mayes, M.D., Stress, M.E., & Yaldao, D.T. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology, 47*, 1396-1402.
- Keller-Wood, M.E., & Dallman, M.F. (1984). Corticosteroid inhibition of ACTH secretion. *Endocrine Reviews, 5*(1), 1-24.
- Kirk, A.D., Mannon, R.B., Swanson, J., & Hale, D.A. (2005). Strategies for minimizing immunosuppression in kidney transplantation. *Transplant International, 18*, 2-14.
- Kirschbaum, C., Wolf, O.T., May, M., Wippich, W., & Hellhammer, D.H. (1996). Stress and treatment induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences, 58*, 1475-1483.
- Klein, R., Klein, B.E., Moss, S. E., Cruickshanks, K.J., & Brazy, P.C. (1999). The 10-year incidence of renal insufficiency in people with type 1 diabetes. *Diabetes Care, 22*, 743-751.

- Knight, E.L., Oesthun, N., Teng, M., Lazarus, M., & Curhan, G.C. (2003). The association between mental health, physical function, and hemodialysis mortality. *Kidney International*, 63, 1843-1851.
- Korbert, S.M., Lewis, E.J., Schwartz, M.M., Reichlin, M., Evans, J., & Rohde, R.D. (2000). Factors predictive of outcome in severe lupus nephritis: Lupus nephritis collaborative study group. *American Journal of Kidney Disease*, 35, 904-914.
- Kovacs, G.L., Telegdy, G., & Lissak, K. 5-hydroxytryptamine and the mediation of pituitary-adrenocortical hormones in the extinction of active avoidance behaviour. *Neuroendocrinology*, 1, 219-230.
- Kramer, L., Madl, C., Stockenhuber, F., Yeganehfar, W., Eisenhuber, E., Derfler, K., et al. (1996). Beneficial effect of renal transplantation on cognitive brain function. *Kidney International*, 49, 833-838.
- Lazzaretti, C.T., Carvalho, J.G.R., Mulinari, R.A., & Rasia, J.M. (2004). Kidney transplantation improves the multidimensional quality of life. *Transplantation Proceedings*, 36, 872-873.
- Lee, S.Y., Lee, H.J., Kim, Y., Kim, S.H, Kim, L., Lee, M.S., et al. (2004). Neurocognitive function and quality of life in relation to hematocrit levels in chronic hemodialysis patients. *Journal of Psychosomatic Research*, 57, 5-10.
- Lengenfelder, J., Chiaravalloti, N.D., Ricker, J.H., & DeLuca, J. (2003). Deciphering components of impaired working memory in multiple sclerosis. *Cognitive and Behavioural Neurology*, 16(1), 28-39.
- Lerut, J.P. (2003). Avoiding steroids in solid organ transplantation. *Transplantation International*, 16, 213-224.
- Levey, A.S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M.W., et al. (2003). National kidney foundation practice guidelines for chronic kidney disease:

- Evaluation, classification, and stratification. *Annals of Internal Medicine*, 139, 137-147.
- Leygoldt, J.K. (2005). Hemodialysis adequacy. In B.J.G. Pereira, M.H. Sayegh, & P. Blake (Eds.), *Chronic kidney disease, dialysis and transplantation*, 2nd Edition (pp. 20-30). Philadelphia, PA: Elsevier & Saunders.
- Li, G., Cherrier, M.M., Tsuang, D.W., Petrie, E.C., Colasurdo, E.A., Craft, S., et al. (2006). Salivary cortisol and memory function in human aging. *Neurobiology of Aging*, 27, 1705-1714.
- Lieberthal, W., & Nigam, S. K. (2000). Acute renal failure II: Experimental models of acute renal failure: Imperfect but indispensable. *American Journal of Renal Physiology*, 278(1), F1-F12.
- Longui, C.A. (2007). Glucocorticoid therapy: Minimizing side effects. *Journal de Pediatria*, 83 (5 Supplement): S163-171.
- Luft, F. C. (2004). Hypertensive nephrosclerosis: Update. *Current Opinion in Nephrology and Hypertension*, 13, 147-154.
- Luine, V.N., Spencer, R.L., & McEwen, B.S. (1993). Effects of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. *Brain Research*, 616, 65-70.
- Lupien, S.J., Lecours, A.R., Lussier, I., Schwartz, G., Nair, N.P.V., & Meaney, M.J. (1994). Basal cortisol levels and cognitive deficits in human ageing. *Journal of Neuroscience*, 14, 2893-2903.
- Lupien, S.J., Lecours, A.R., Schwartz, G., Scharma, S., Hauger, R.L., Meaney, M.J., et al. (1996). Longitudinal study of basal cortisol levels in healthy elderly subjects: Evidence for subgroups. *Neurobiology of Aging*, 17(1), 95-105.
- Lupien, S.J., DeLeon, M., DeSanti, S., Convit, A., Tarshish, C., Nair, N.P.V., et al. (1997). Stress-induced declarative memory impairment in healthy elderly subjects:

- relationship to cortisol reactivity. *Journal of Clinical Endocrinology and Metabolism*, *82*, 2070-2075.
- Lupien, S.J., & McEwen, B.S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews*, *24*, 1-27.
- Lupien, S.J., DeLeon, M., DeSanti, S., Convit, A., Tarshish, C., Nair, N.P.V., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, *1*(1), 69-73.
- Lupien, S.J., Gillin, C.J., & Hauger, R.L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose response study in humans. *Behavioural Neuroscience*, *113*(3), 420-430.
- Lupien, S.J., & LePage, M. (2001). Stress, memory, and the hippocampus: Can't live with it, can't live without it. *Behavioural Brain Research*, *127*, 137-158.
- Lupien, S.J., Wilkinson, C.W., Briere, S., Menard, C., Kin, N.M.K., & Nair, N.P.V. (2002a). The modulatory effects of corticosteroids on cognition: Studies in young human populations. *Psychoneuroendocrinology*, *27*, 401-416.
- Lupien, S.J., Wilkinson, C.W., Briere, S., Ng Ying, Kin, N.M.K., Meaney, M.J., & Nair, N.P.V. (2002b). Acute modulation of aged human memory by pharmacological manipulation of glucocorticoids. *Journal of Clinical Endocrinology and Metabolism*, *87*, 3798-3807.
- Lysaght, M.J. (2002). Maintenance dialysis population dynamics: Current trends and long-term implications. *Journal of the American Society of Nephrology*, *13*, S37-S40.
- MacLulich, A.M.J., Deary, I.J., Starr, J.M., Ferguson, K. J., Wardlaw, J.M., & Seckl, J.R. (2005). Plasma cortisol levels, brain volumes and cognition in healthy elderly men. *Psychoneuroendocrinology*, *30*, 505-515.

- Magee, C.C. (2005). Evaluation of donors and recipients. In B.J.G. Pereira, M.H. Sayegh, & P. Blake (Eds.), *Chronic kidney disease, dialysis, and transplantation* (pp. 623-631). Philadelphia, PA: Elsevier & Saunders.
- Margarinos, A.M., & McEwen, B.S. (1995). Stress-induced atrophy of apical dendrites of hippocampal CA3 neurons: Involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience*, *69*, 89-98.
- Marsh, J.T., Brown, W.S., Wolcott, D., Carr, C.R., Harper, R., Schweitzer, S.V., et al. (1991). rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney International*, *39*, 155-163.
- Marshall, R.D., & Garakani, A. (2002). Psychobiology of the acute stress response and its relationship to the psychobiology of post-traumatic stress disorder. *Psychiatric Clinics of North America*, *25*, 385-395.
- Martignoni, E., Costa, A., Sinforiani, E., Liuzzi, A., Chiodini, P., Mauri, M., et al. (1992). The brain as a target for adrenocortical steroids: Cognitive implications. *Psychoneuroendocrinology*, *17*(4), 343-354.
- Martin, R.D. (1990). *Primate origins and evolution*. London: Chapman and Hall.
- Martins, D., Tareen, N., & Norris, K.C. (2002). The epidemiology of end-stage renal disease among African-Americans. *American Journal of Medical Sciences*, *323*, 65-71.
- Maschio, G., Marcantoni, C., & Bernich, P. (1999). Systemic hypertension and antihypertensive agents. *Journal of Nephrology*, *12*(Suppl. 2), S100-104.
- Mason, J.W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosomatic Medicine*, *30*, 576-607.
- McAllister, T.W., Saykin, A.J., & Flashman, L.A. (1999). Brain activation during working memory one month after mild traumatic brain injury: A functional MRI study. *Neurology*, *53*, 1300-1308.

- McCormick, C.M., Lewis, E., Somley, B., & Kahan, T.A. (2007). Individual differences in cortisol levels and performance on a test of executive function in men and women. *Physiology and Behaviour, 91*, 87-94.
- McEwen, B.S., Gould, E.A., & Sakai, R.R. (1992). The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *British Journal of Psychiatry, 160* (suppl. 15), 18-24.
- McEwen, B.S., Weiss, J.M., & Schwartz, L.S. (1968). Selective retention of corticosterone by limbic structure in rat brain. *Nature, 220*, 911-920.
- McKee, D.C., Burnett, G.B., Raft, D.D., Batten, P.G., & Bain, K.P. (1982). Longitudinal study of neuropsychological functioning in patients on chronic hemodialysis: A preliminary report. *Journal of Psychosomatic Research, 26*(5), 511-518.
- Mitrushina, M.N., Boone, K.B., & D'Elia, L.F. (1999). *Handbook of normative data for neuropsychological assessment*. New York: Oxford University Press.
- Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., & Howerter, A. (2000). The unity and diversity of Executive Functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*, 49-100.
- Mohanram, A., & Toto, R.D. (2005). Measurement of kidney function. In B.J.G. Pereira, M.H. Sayegh, & P. Blake (Eds.), *Chronic kidney disease, dialysis and transplantation, 2nd Edition* (pp. 20-30). Philadelphia, PA: Elsevier & Saunders.
- Monastero, R., Camarda, C., Pipia, C., Lopez, G., Camarda, L.K.C., Baiamonte, V., Ferrante, A., Triolo, G., & Camarda, R. (2004). Cognitive impairment in behcet's disease patients without overt neurological involvement. *Journal of the Neurological Sciences, 220*, 99-104.
- Muirhead, N. (2001). The rationale for early management of chronic renal insufficiency. *Nephrology, Dialysis, Transplantation, 16 Suppl 7*, 51-56.

- Murawski, B.J. (1975). Psychological approaches to study the uremic state. *Kidney International*, 2(Suppl.), 206-209.
- National High Blood Pressure Education Program (NHBEP). (2003). Outcomes related to varying levels of hypertensive states in the US populations with ESRD. *Hypertension*, 42, S12-25.
- National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) (2002). Advisory Board: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Kidney disease outcome quality initiative. *American Journal of Kidney Disease*, 39 (2 Suppl. 2): S1-S246.
- Nesbitt, K. (2004). An overview of diabetic nephropathy. *Journal of Pharmacy Practice*, 17(1), 75-79.
- Nesrallah, G.E., Blake, P.G., & Mendelssohn, D.C. (2005). Modality options for end-stage renal disease care. In B.J.G. Pereira, M.H. Sayegh, & P. Blake (Eds.), *Chronic kidney disease, dialysis and transplantation, 2nd Edition* (pp. 279-300). Philadelphia, PA: Elsevier & Saunders.
- Newcomer, J.W., Craft, S., Hershey, T., Askins, K., & Bardgett, M.E. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *The Journal of Neuroscience*, 14(4), 2047-2053.
- Newcomer, J.W., Selke, G., Melson, A.K., Hershey, T., Craft, S., Richards, K., et al. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry*, 56, 527-533.
- O'Callaghan, C.A. (2004). Renal manifestations of systemic autoimmune disease: Diagnosis and therapy. *Best Practices & Research in Clinical Rheumatology*, 18(3), 411-427.
- Obrador, G.T., Pereira, B. J., & Kausz, T. (2002). Chronic kidney disease in the United States: An under-recognized problem. *Seminars in Nephrology*, 22(6), 441-448.

- Oitzl, M.S., & DeKloet, E.R. (1992). Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behavioural Neuroscience*, *106*, 62-71.
- Osberg, J.W., Meares, G.J., McKee, D.C., & Burnett, G.B. (1982). Intellectual functioning in renal failure and chronic dialysis. *Journal of Chronic Disability*, *35*, 445-457.
- Pascual, M., Theruvath, T., Kawai, T., Rubin, N., & Cosimi, B. (2002). Strategies for improving long-term outcomes after renal transplantation. *The New England Journal of Medicine*, *346*(8), 580-590.
- Pavlidis, C., Watanabe, Y., & McEwen, B.S. (1993). Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus*, *3*(2), 183-192.
- Pease, R. W. (Ed.). (2002). *Merriam-Webster's medical desk dictionary (Revised Edition)*. Merriam-Webster's Incorporated.
- Pedhazur, E.J. (2002). *Multiple regression in behaviour research*. Philadelphia: Harcourt Incorporated.
- Pereira, A.A., Weiner, D.E., Scott, T., Chandra, P., Bluestein, R., Griffith, J., et al. (2007). Subcortical cognitive impairment in dialysis patients. *Hemodialysis International*, *11*, 309-314.
- Plihal, W., Krug, R., Pietrowsky, R., Fehm, H.L., & Born, J. (1996). Corticosteroid receptor mediated effects on mood in humans. *Psychoneuroendocrinology*, *21*(6), 515-523.
- Pliskin, N.H., Kolbasa, T.A., Hart, R.P., & Umans, J.G. (2001). Neuropsychological function in renal disease and its treatment. In Tarter et al., (Eds.), *Medical neuropsychology, 2nd Edition*, (pp. 107-126). New York: Kluwer Academic/Plenum Publishers.

- Pliskin, N.H., Yurk, H.M., Ho, T., & Umans, J.G. (1996). Neurocognitive function in chronic hemodialysis patients. *Kidney International*, *49*, 1435-1440.
- Pontremoli, R., Leoncini, G., Ravera, M., Viazzi, F., Vettoretti, S., Ratto, E., et al. (2002). Microalbuminuria, cardiovascular, and renal risk in primary hypertension. *Journal of the American Society of Nephrology*, *13*, S169-S172.
- Prasad, R.V., Nash, M.M., McFarlane, P.A., & Zaltzman, J.S. (2003). Renal transplant recipient attitudes toward steroid use and steroid withdrawal. *Clinical Transplantation*, *17*, 135-139.
- Pusey, C.D., Rees, A.J., & Evans, D.J. (1991). Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney International*, *40*, 757-763.
- Regard, M. (1981). *Cognitive rigidity and flexibility: A neuropsychological study*. Unpublished doctoral dissertation, University of Victoria, Canada.
- Reitan, R.M., & Wolfson, D. (1994). A selective and critical review of neuropsychological deficits and the frontal lobes. *Neuropsychology Review*, *4*, 161-197.
- Reitan, R.M., & Wolfson, D. (1985). *The Halstead-Reitan neuropsychological test battery*. Tucson AZ: Neuropsychology Press.
- Ritz, E., & Orth, S.R. (1999). Nephropathy in patients with type II diabetes mellitus. *The New England Journal of Medicine*, *341*(15), 1127-1133.
- Rome, H.P., & Braceland, F.L. (1952). The psychological response to ACTH, cortisone, hydrocortisone, and related steroid substances. *American Journal of Psychiatry*, (March), 641-651.
- Roosendaal, B. (2000). Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology*, *25*, 213-238.
- Ryan, J.J., Souheaver, G.T., & DeWolfe, A.S. (1981). Halstead-Reitan test results in chronic hemodialysis. *The Journal of Nervous and Mental Disease*, *169*, 311-314.

- Sandi, C., & Rose, S.P.R. (1994). Corticosterone enhances long-term retention in one-day old chicks trained in a weak passive avoidance learning paradigm. *Brain Research*, *647*, 106-112.
- Sandi, C., & Rose, S.P.R. (1997). Training-dependent biphasic effects of corticosterone in memory formation for a passive avoidance task in chicks. *Psychopharmacology*, *133*, 152-160.
- Sapolsky, R.M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*, 925-935.
- Sapolsky, R.M., Krey, L.C., & McEwen B.S. (1986). The Neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocrine Reviews*, *7*(3), 284-301.
- Saykin, A.J., Johnson, S.C., & Flashman, L.A. (1999). Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: An fMRI study. *Brain*, *122*, 1963-1971.
- Schaubel, D.E., Morrison, H.I., Desmeules, M., Parsons, D., & Fenton, S.A. (1998). End-stage renal disease projections for Canada to 2005 using Poisson and Markov models. *International Journal of Epidemiology*, *27*, 274-281.
- Schmidt, L.A., Fox, N.A., Goldberg, M.C., Smith, C.C., & Schulkin, J. (1999). Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. *Psychoneuroendocrinology*, *24*, 461-483.
- Schmidt, M., (1996). *The Rey Auditory Verbal Learning Test*. Philadelphia, PA: Western Psychological Services Inc.
- Seeman, T.E., McEwen, B.S., Singer, B.H., Albert, M.S., & Rowe, J.W. (1997). Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *Journal of Clinical Endocrinology and Metabolism*, *82*(8), 2458-2465.

- Shumway, J.T., & Gambert, S.R. (2002). Diabetic nephropathy-pathophysiology and management. *International Urology and Nephrology*, *34*, 257-264.
- Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests: Second edition*. New York: Oxford University Press.
- Squire, L.R., (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of learning and Memory*, *82*, 171-177.
- Starkman, M.N., Gebarski, S.S., Berent, S., & Scheingart, D.E. (1992). Hippocampal formation volume, memory dysfunction and cortisol levels in patients with cushing's syndrome. *Biological Psychiatry*, *32*, 756-765.
- Starkman, M.N., Giordani, B., Berent, S., Schork, A., & Scheingart, D.E. (2001). Elevated cortisol levels in cushing's disease are associated with cognitive decrements. *Psychosomatic Medicine*, *63*, 985-993.
- Starkman, M.N., Giordani, B., Gebarski, S.S., & Scheingart, D.E. (2003). Improvement in learning associated with an increase in the hippocampal formation volume. *Biological Psychiatry*, *53*(3), 233-238.
- Stengel, B., Billon, S., Paul, C.W., Jager, K.J., Dekker, F.W., et al. (2003). Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990-1999. *Nephrology, Dialysis, Transplantation*, *18*, 1824-1833.
- Strauss, E., Sherman, M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests*. New York: Oxford University Press.
- Stuss, D.T., & Benson, D.F. (1986). *The frontal lobes*. New York: Raven Press.
- Suthanthiran, M., & Strom, T.B. (1994). Renal transplantation. *The New England Journal of Medicine*, *331*, 365-376.
- Teschan, P.E., Ginn, E., Bourne, J.R., Ward, J.W., Hamel, B., Nunnally, J.C., et al. (1979). Quantitative indices of clinical uremia. *Kidney International*, *15*, 676-697.

- Tulving, E., & Markowitsch, H.J. (1997). Memory beyond the hippocampus. *Current Opinion in Neurobiology*, 7, 209-216.
- U.S. Renal Data System. (2000). Annual data report: *Atlas of end-stage renal disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2000.
- Umans, J.G., & Pliskin, N.H. (1998). Attention and mental processing speed in hemodialysis patients. *American Journal of Kidney Diseases*, 32(5), 749-751.
- Van der Beek, E.M., Wiegant, V.M., Schouten, W.G.P., van Eerdenburg, F.J.C.M., Loijens, L.W.S., van der Plas, C., et al. (2004). Neuronal number, volume, and apoptosis of the left dentate gyrus of chronically stressed pigs correlate negatively with basal saliva cortisol levels. *Hippocampus*, 14(6), 688-700.
- Vedhara, K., Hyde, J., Gilchrist, I.D., Tytherleigh, M., & Plummer, S. (2000). Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology*, 25, 535-549.
- Vincenti, F. (2004). A decade of progress in kidney transplantation. *Transplantation*, 77, S52-61.
- Vollman-Honsdorf, G.K., Flugge, G., & Fuchs, E. (1997). Chronic psychosocial stress does not affect the number of pyramidal neurons in the tree shrew hippocampus. *Neuroscience Letters*, 233, 121-124.
- Waltman, C., Blackman, M.R., Chrousos, G.P., Reiman, C., & Harman, S.M. (1991). Spontaneous and glucocorticoid-inhibited adrenocorticotrophic hormone and cortisol secretion are similar in healthy young and old men. *Journal of Clinical Endocrinology and Metabolism*, 73, 495-502.
- Watts, R.A., Carruthers, D.M., & Scott, D.G. (1995). Epidemiology of systemic vasculitis: Changing incidence or definition? *Seminars in Arthritis and Rheumatism*, 25, 28-34.

- Wechsler, D. (1997). *The Wechsler Adult Intelligence Scales- 3rd Edition (WAIS-III)*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D., (1997). *The Wechsler Memory Scales-3rd Edition (WMS-III)*. San Antonio, TX: The Psychological Corporation.
- West, M. (1993). Regionally specific loss of neuron in the aging human hippocampus. *Physiology of Aging, 14*, 287-293.
- Wilkinson, G. S. (1993). *WRAT-3: Wide Range Achievement Test administration manual (3rd ed.)*. Wilmington, DE: Western Psychological Services.
- Williams, M.A., Sklar, A.H., Burrett, R.G., & Donovan, P.J. (2004). Temporal effects of dialysis on cognitive functioning in patients with ESRD. *American Journal of Kidney Diseases, 43*(4), 705-711.
- Wolcott, D.L., Wellisch, D.K., Marsh, J.T., Schaeffer, J., Landsverk, J., & Nissenson, A.R. (1988). Relationship of dialysis modality and other factors to cognitive function in chronic dialysis patients. *American Journal of Kidney Diseases, 12*(4), 275-284.
- Wolkowitz, O.M. (1994). Prospective controlled studies of the behavioural and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology, 19*(3), 233-255.
- Wolkowitz, O.M., Reus, V.I., Weingartner, H., Thompson, K., Breier, A., Doran, A., et al. (1990). Cognitive effects of corticosteroids. *American Journal of Psychiatry, 147*(10), 1297-1303.
- Yeun, J.Y., & Depner, T.A. (2005). Principles of hemodialysis. In B.J.G., Pereira, M.H., Sayegh, & P. Blake (Eds.), *Chronic kidney disease, dialysis and transplantation, 2nd Edition* (pp. 307-341). Philadelphia, PA: Elsevier & Saunders.
- Young, A.H., Sahakian, B.J., Robbins, T.W., & Cowen, P.J. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology, 145*, 260-266.

Young, C.J., & Gaston, R.S. (2000). Renal transplantation in Black Americans. *New England Journal of Medicine*, 21(343), 1545-1552.

Table 1

National Kidney Foundation Kidney Disease Outcomes Initiative Classification (K/DOQI) of Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m ² bsa)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

Note. GFR = Glomerular Filtration Rate.

Note. Information for table adapted from K/DOQI Guidelines 2002.

Table 2

Description of all the tests administered as part of the protocol

<p>Brief Symptom Inventory (BSI) (Derogatis, 1983)</p> <p>The BSI is a 53 item psychiatric screening tool frequently utilized in clinical settings. This self-report instrument generates 9 primary symptom dimensions and three global indices, of which one is the global severity index.</p>
<p>Wide Range Achievement Test- 3rd Edition (Wilkinson, 1993)- (WRAT-3) Reading Subtest.</p> <p>The reading subtest requires the subject to pronounce words out of context, and may require them to pronounce letters out of context. The total score is the number of words correctly pronounced.</p>
<p>Wechsler Memory Scale- 3rd Edition, (WMS-III) Logical Memory I and II (LMI and LMII) (Wechsler, 1997)</p> <p>This is a test of declarative memory. The first section (LMI) requires the subject to listen to a story read aloud and immediately recall as much as he/she can remember. This procedure is repeated for a second story. After a 20 to 25 minute delay, during which other tests are administered, the subject is administered LMII during which he/she must recall as much as he/she can remember from the two stories. The subject is then administered a forced choice recognition test and must choose from two elements, one of which was in the initial stories. The score for the immediate and delayed recall trials is the number of story elements correctly recalled, whereas the score for recognition is the number of elements correctly identified.</p>
<p>Rey Auditory Verbal Learning Test, (RAVLT) (Schmidt, 1996)</p>

This is a test of declarative memory. The subject is read aloud a list of 15 words, and must repeat back as many as he/she can remember. This list (list A) is administered four more times and each time the subject repeats back what can be remembered. The subject is then read a different list of words (list B), and must recall as many words from this new list as he/she can remember. After this, the subject is asked to recall as many words as possible from list A (short-delayed recall). After a 20-25 minute delay, the subject is asked to recall all the words he/she can remember from list A (long-delayed recall). Finally a list is presented to the subject containing words from list A, list B, and several foils. The subject must identify words from list A and list B (recognition). Total score for the recall sections is the number of words correctly recalled. Total score for recognition is the number of words correctly recognized. A discriminability score is calculated that represents the ratio of words from list A correctly recognized relative to foil words that are endorsed.

Trail Making Test Part A, (TMTA) (Reitan, 1985)

This is a test of simple attention. The subject is asked to draw a line connecting a series of numbers in numerical order as quickly as possible. Total score is time to complete. Number of errors is also recorded.

Wechsler Adult Intelligence Scale- 3rd Edition, (WAIS-III)- Digit Span Subtest (Wechsler, 1997)

This is a test of attention. The subject is read aloud a series of numbers of progressively longer lengths. After each series is read, the subject must recall the series in the correct order. The test is discontinued either after all items are administered, or after the subject commits errors on all three trials of an item. The subject is then read aloud a series of numbers of progressively longer lengths in reverse numerical order, after which he/she is asked to recall as many as possible. The total score is the number of series correctly

recalled.

Stroop Colour Word Test- Victoria Version (Regard, 1981)

This is a test of inhibition and disinhibition. Three cards are presented to the participant: D, W, and C. With card D the participant must name as quickly as possible the colour of 24 dots printed in blue, green, red, or yellow. Each colour is used six times, and the four colours are arranged in pseudo-random order within the array, each colour appearing once in each row. Card W is similar to D except the dots are replaced by common words (when, hard, and over), printed in lower-case letters. The participant must name the colour of the words but ignore their content. Card C is similar to cards D and W except the coloured stimuli are the colour names "blue, green, red and yellow" printed in lower case letters, so the print colour never corresponds with the colour name. Participants are required to name the colours in which the words are printed. The total score is the time to completion for each card, and the total number of errors.

WAIS-III- Letter-Number Sequencing Subtest (Wechsler, 1997)

This is a test of working memory capacity. The subject is read aloud a series of numbers and letters in mixed series. The subject must recall each series after presentation, but produce numbers first in ascending order followed by letters in alphabetical order. The series get longer as the test progresses. The test is discontinued either after administration of all the items, or after the subject commits errors on all three trials of any item. The total score is the number of series correctly recalled.

Trail Making Test Part B, (TMTB) (Reitan, 1985)

This test is thought to assess cognitive set-shifting. It is a paper and pencil task that requires the subject to connect a series of numbers and letters, alternating between the two. The letters must be connected in alphabetical order and the numbers in ascending

order. For example, the subject is asked to start at the number 1 and draw a line to A then to 2 then to B, 3, C etc. until they reach the circle, marked end. The total score is the time to completion. Total number of errors is recorded.

Auditory N-Back Test (adapted from Lengenfelder et al., 2003)

The N-back test is thought to be a sensitive measure of working memory capacity (Saykin, Johnson, & Flashman, 1999; McAllister, Saykn, & Flashman, 1999). The auditory version requires the subject to listen to a string of consonant letters presented auditorily every 3 seconds via cassette tape. Three conditions are presented: 0-back, 1-back, and 2-back. There are two blocks of five trials for each condition. In the 0-back condition, the subject is asked to decide whether a certain letter matches a single target letter that is previously specified by tapping on the table when the target letter is heard. In the 1-back condition the participant must decide whether a presented letter matches the one just preceding it by tapping on the table. The 2-back condition requires the participant to indicate via table tap whether a presented letter matches one 2-back in the sequence. The score is the total number of errors made in each condition.

WAIS-III, Digit-Symbol Coding Subtest (Wechsler, 1997)

This is a test of processing speed and requires the subject to complete a series of boxes, by filling in the symbol that corresponds with the number in the top half of the box as quickly as possible (the numbers are in scrambled order). They use a grid presented at the top of the page. The total score is the time to completion.

WMS-III, Spatial Span Subtest (Wechsler, 1997)

This is a test of attention and non-verbal working memory. The subject is presented with a form board containing a number of coloured blocks. The examiner outlines specific patterns by touching various blocks. After this, the subject is required to tap the same blocks. The series again, get progressively longer as the test goes on. Following this

the subject is required to tap the blocks in the reverse order of that demonstrated by the examiner. The subtest is discontinued when the subject commits errors on all three trials of an item. The total score is the number of series correctly recalled for both forward and backward procedures.

WAIS-III, Symbol Search Subtest (Wechsler, 1997)

This is a test of processing speed and visual scanning. The subject is required to indicate whether either of two symbols presented on the right side of the page match a series of symbols on the left side. They are required to complete the test as quickly as they can without skipping any items. Total time is 120 seconds, and the total score is the number correct minus the number incorrect.

CAGE4

This is a four item screening measure for alcohol abuse. The questions assess whether the subject has attempted to cut-down on his/her alcohol consumption unsuccessfully, whether he/she gets annoyed when reminded of his/her habit, whether he/she feels guilty after he/she has drunk, and whether the subject has used alcohol as an eye opener.

Table 3

Tests comprising each composite category

Declarative Memory
-WMS-III Logical Memory I (total correct)
-WMS-III Logical Memory II (total correct)
-RAVLT (total words trials 1-5)
-RAVLT (20-minute delayed recall)
-RAVLT (discriminability)
Complex Attention
-TMTB (time to completion)
-TMTB (errors)
-Stroop Colour Word Test (colour-word trial time to completion)
-Stroop Colour Word Test (colour-word trial errors)
-Auditory N-Back Test (1-back total errors)
-Auditory N-Back Test (2-back condition total errors)
-WAIS-III Letter-Number Sequencing (total correct)
-WAIS-III Digit Span backward (total correct)
-WMS-III Spatial Span backward (total correct)

Simple Attention

- WAIS-III Digit Span forward (total correct)
- WMS-III Spatial Span forward (total correct)
- Auditory N-Back Test (0-back condition total errors)
- TMTA (time to completion)

Processing Speed

- WAIS-III Digit-Symbol Coding subtest (total correct)
- WAIS-III Symbol Search subtest (correct-incorrect)
- Stroop Colour Word Test (colour naming trial time to completion)
- Stroop Colour Word Test (word reading trial time to completion)

Note. Text in bold represents the Cognitive Composite domain.

WMS-III = Wechsler Memory Scale 3rd Edition

WAIS-III = Wechsler Adult Intelligence Scale 3rd Edition

RAVLT = Rey Auditory Verbal Learning Test

TMTB = Trail Making Test Part B

TMTA = Trail Making Test Part A

Table 4

Descriptive information and group-wise comparisons for demographic and clinical variables for participants in the steroid avoidance (SA) and chronic steroid (CS) groups

Variable	SA (n=22)	CS (n=17)	Test Statistic	Significance (p)
Age (months)	537 (233-728)	504 (256-684)	$t = .82$.42
Gender (male/female)	16/6 (72.7%/27.3%)	8/9 (47.1%/52.9%)	$\chi^2 = 2.67$.10
Handedness (right/left)	20/2 (90.9%/9.1%)	15/2 (88.2%/11.8%)	$\chi^2 = .07$.79 (1.0)
Ethnicity				
European American	10 (45.5%)	4 (23.5%)	$\chi^2 = 2.00$.16 (.19)
African American	10 (45.5%)	12 (70.6%)	$\chi^2 = 2.46$.12
Asian American	1 (4.5%)	0		
Other	1 (4.5%)	1 (5.9%)		
ESRD Etiology				
Hypertension	15 (68.2%)	7 (41.2%)	$\chi^2 = 2.84$.09
Diabetes	1 (4.5%)	3 (17.6%)		
Hypertension+Diabetes	5 (22.7%)	5 (29.4%)		
Other	1(4.5%)	2 (11.8%)		
Type of Transplant				
Cadaveric	15 (68.2%)	12 (70.6%)	$\chi^2 = .03$.87
Living related donor	7(31.8%)	4 (23.5%)		
Living unrelated donor	0	1(5.9%)		
Type of Dialysis Prior to Transplant				
None	2 (9.1%)	1(5.9%)		
Hemodialysis	14 (63.6%)	12 (70.6%)	$\chi^2 = .21$.65
Peritoneal dialysis	4 (18.2%)	3 (17.6%)		
Both	2 (9.1%)	1(5.9%)		
Antihypertensive Treatment				
Beta Blockers	11(50%)	11(64.7%)	$\chi^2 = .84$.36

Other antihypertensives	10 (45%)	13 (76%)		
Years of education	12.8 (10-18)	13.9 (12-18)	<i>t</i> = 2.6	.01
GFR (ml/min.1.73m ²)	67.4 (40-105.4)	64.1 (40-107.7)	<i>t</i> = .53	.60
Systolic blood pressure (mm Hg)	132.1 (104-165)	135.2 (105-155)	<i>t</i> = .90	.33
Diastolic blood pressure (mm Hg)	80.3 (70-98)	77.9 (64-97)	<i>t</i> = .72	.48
Months since transplant	19.8 (6-51)	27.4 (6-70)	<i>t</i> = 1.64	.11
Duration of Dialysis (months)	47 (0-170)	50.7 (0-104)	<i>U</i> = 156.0	.39
mycophenolate mofetil dose/day (mg)	1765 (1080-3000)	1374.7 (1000-2000)*	<i>U</i> = 85.0	.00*
tacrolimus dose/day (mg)	9.3 (1.5-16)	7.3 (2-18)	<i>U</i> = 79.0	.41
WRAT-3 Reading Score	87.8 (60-111)	92.0 (64-107)	<i>U</i> = 151.0	.32
BSI (GSI)	50.7 (33-65)	51.3 (33-60)	<i>t</i> = .25	.81

Note. For continuous variables numbers in parentheses are ranges.

Numbers in italics are values associated with Fisher's exact test.

t = one-tailed independent samples t-statistic.

U = one-tailed independent samples Mann-Whitney U statistic.

*X*² = Chi-squared statistic.

GFR = Glomerular Filtration Rate.

WRAT-3 Reading Score = Wide Range Achievement Test 3rd Edition, Reading Subtest Standard Score.

BSI (GSI) = Brief Symptom Inventory (Global Severity Index) T-score.

mm Hg = millimeters of mercury.

**p* < .05, after adjusting for multiple comparisons.

Table 5

Age-adjusted scaled scores and age-adjusted t-scores on neuropsychological tests for participants in the steroid avoidance and chronic steroid groups

Test Score	Steroid Avoidance (n=22)	Chronic Steroid (n=17)
Digit Span	8.4 (2.3)	9.6 (2.9)
Letter-Number Sequencing	8.5 (2.6)	10.0 (2.1)
Digit Symbol Coding	8.7 (3.1)	9.7 (3.3)
Symbol Search	9.1 (2.9)	9.8 (3.3)
Logical Memory I	9.1 (2.1)	9.4 (2.8)
Logical Memory II	10.2 (2.4)	10.7 (2.7)
Spatial Span	9.2 (2.6)	9.3 (2.6)
RAVLT (Total 1-5)	49.3 (14.2)	50.4 (12.7)
RAVLT (Delayed)	49.8 (11.8)	50.6 (12.1)
Stroop Dots (time)	51.9 (11.1)	50.2 (10.8)
Stroop Words (time)	49.3 (11.0)	47.6 (11.3)
Stroop Colour-Word (time)	47.4 (11.4)	51.9 (6.5)
TMTA (time)	49.7 (9.4)	53.5 (7.7)
TMTB (time)	51.6 (9.5)	54.5 (6.7)

Note. Numbers in parentheses are standard deviations.

RAVLT (Total 1-5) = Rey Auditory Verbal Learning Test total words trials 1-5.

RAVLT (Delayed) = Rey Auditory Verbal Learning Test delayed recall.

TMTA (time) = Trail Making Test Part A time to completion in seconds.

TMTB (time) = Trail Making Test Part B time to completion in seconds.

Scores for Digit Span, Letter-Number Sequencing, Digit Symbol Coding, Symbol Search, Logical Memory I, Spatial Span, and Logical Memory II, are scaled scores each with a mean of 10 and a standard deviation of 3.

Scores for RAVLT (Total 1-5), RAVLT (Delayed), Stroop Dots (time), Stroop Words (time), Stroop Colour-Word (time), TMTA (time), and TMTB (time), are t-scores each with a mean of 50 and a standard deviation of 10.

Table 6

Published normative data used to derive age-based scaled scores and t-scores

Normative Data Set	Test Scores
WAIS-III Administration Manual (Wechsler, 1997)	Digits Span Letter-Number Sequencing Digit Symbol Coding Symbol Search
WMS-III Administration Manual (Wechsler, 1997)	Logical Memory I Logical Memory II Spatial Span
Geffen, Moar, O'Hanlon, Clark & Geffen (as cited in Mitrushina, Boone, & D'Elia, 1999)	RAVLT (Total 1-5) RAVLT (Delayed)
Tombaugh, Rees & McIntyre (as cited in Spreen & Strauss, 1998)	TMTA (time) TMTB (time)
Bullock, Brulot & Strauss (as cited in Spreen & Strauss, 1998)	Stroop Dots (time) Stroop Words (time) Stroop Colour-Word (time)

Note. WAIS-III = Wechsler Adult Intelligence Scale- 3rd Edition.

WMS-III = Wechsler Memory Scale- 3rd Edition.

RAVLT (Total 1-5) = Rey Auditory Verbal Learning Test total words trials 1-5.

RAVLT (Delayed) = Rey Auditory Verbal Learning Test delayed recall.

TMTA (time) = Trail Making Test Part A time to completion in seconds.

TMTB (time) = Trail Making Test Part B time to completion in seconds.

Table 7

Spearman's correlations for each of the continuous demographic and medical variables with the four cognitive composite scores

Variable	DECOM	SIMAT	COMAT	PS
Age (months)	.19 (.24)	<i>.14 (.88)</i>	-.20 (.23)	-.22 (.19)
Education (years)	.30 (.06)	.21 (.20)	.36 (.02)	.19 (.23)
WRAT-3 Reading	.49 (.01)	.31 (.05)	.55 (.00)*	.31 (.02)
Systolic Blood Pressure	-.13 (.43)	.11 (.51)	-.15 (.36)	.01 (.94)
Diastolic Blood Pressure	.05 (.77)	.14 (.38)	.02(.92)	.02(.90)
MMF dose per day (mg)	.03 (.86)	-.32 (.05)	-.17 (.31)	-.06 (.70)
Duration of Dialysis (months)	-.37 (.02)	-.16 (.34)	-.40 (.01)	-.57 (.00)*
Months since Transplant	.25 (.12)	.42 (.01)	.43 (.01)	.27 (.09)
GFR	.08 (.64)	.02 (.86)	.05 (.75)	.03 (.86)
BSI (GSI) score	-.15 (.36)	-.07 (.68)	-.07 (.67)	-.23 (.15)
tacrolimus dose per day (mg)	-.12 (.54)	-.21 (.27)	-.28 (.14)	-.24 (.21)

Note. The italicized number represents the value of eta and the corresponding p -value.

DECOM = Declarative memory composite score.

SIMAT = Simple attention composite score.

COMAT = Complex attention composite score.

PS = Processing speed composite score.

GFR = Glomerular Filtration Rate (ml/min/1.73m²).

BSI (GSI) = Brief Symptom Inventory (General Severity Index) raw score.

WRAT-3 Reading = Wide Range Achievement Test- 3rd Edition, reading subtest raw score.

MMF = mycophenolate mofetil.

Systolic and diastolic blood pressure values are in millimeters of mercury.

* $p < .05$, after adjustment for multiple correlations.

Table 8

Z-scores and group-wise comparisons for each of the tests used to form the cognitive composite scores for participants in the steroid avoidance (SA) and chronic steroid (CS) groups

Domain/Test Score	SA (n=22)	CS (n=17)	Test Statistic	Significance (<i>p</i>)
Declarative Memory				
WMS- LMI	-.02(.76)	.03(.86)	<i>t</i> = .19	.42
WMS-LMII	-.06(.93)	.08(1.1)	<i>t</i> = .42	.34
RAVLT (1-5)	-.08(.94)	.10(1.1)	<i>t</i> = .56	.29
RAVLT Long Delay	-.14(1.0)	.18(.92)	<i>t</i> = .97	.17
Discriminability	-.06(1.0)	.07(.99)	<i>t</i> = .40	.34
Simple Attention				
Digit Span Forward	.22(.87)	-.29(1.1)	<i>U</i> = 125	.04
Spatial Span Forward	-.18(.54)	.23(.45)	<i>t</i> = 2.52	.02*
TMT Part A	-.16(.99)	.21(1.0)	<i>t</i> = 1.2	.12
0-Back Condition	-.20(1.0)	.26(.90)	<i>U</i> = 150	.15
Complex Attention				
Digit Span Backward	-.23(1.1)	.29(.84)	<i>t</i> = 1.7	.05
Spatial Span Backward	-.12(1.3)	.16(.00)	<i>U</i> = 178.5	.41
Letter Number Sequencing	-.12(.52)	.15(.51)	<i>F</i> = .94	.34
Stroop Colour-Word	-.25(.72)	.33(1.2)	<i>t</i> = 1.9	.04
Stroop Colour-Word Errors	.18(.97)	-.24(1.0)	<i>t</i> = 1.3	.10
TMT Part B	-.32(.99)	.41(.87)	<i>t</i> = 2.4	.01
	-.23(1.1)	.30(.80)	<i>t</i> = 1.7	.04
	-.06(1.0)	.07(1.0)	<i>U</i> = 164	.26
	-.22(1.0)	.29(.87)	<i>U</i> = 152.5	.17

TMT Part B Errors	-.05(1.1)	.07(.81)	$U = 186$.49
1-Back Condition	.09(.83)	-.11(1.2)	$U = 180$.43
2-Back Condition	-.20(1.0)	.25(.97)	$U = 132.5$.06
Processing Speed	-.05(.88)	.06(.77)	$U = 18$.49
Digit Symbol Coding	-.18(.94)	.23(1.0)	$t = 1.3$.10
Symbol Search	-.12(1.1)	.17(.91)	$t = .91$.18
Stroop Dots time	.06(1.0)	-.08(.96)	$U = 163$.26
Stroop Words time	.05(1.0)	-.07(1.0)	$t = .37$.36

Note. t = one-tailed independent samples t-test.

U = Mann-Whitney U test.

F = Results of univariate ANCOVA with years of education as a covariate.

WMS-LMI = Wechsler Memory Scale- Logical Memory I.

WMS-LMII = Wechsler Memory Scale-Logical Memory II.

RAVLT (1-5) = Rey Auditory Verbal Learning Test total words trials 1-5.

RAVLT Long Delay = Rey Auditory Verbal Learning Test 20-minute delayed recall.

Discriminability = Rey Auditory Verbal Learning Test discriminability.

TMT Part A = Trail Making Test part A time to completion in seconds.

TMT Part B = Trail Making Test part B time to completion in seconds.

TMT Part B Errors = Trail Making Test part B total errors.

0-Back Condition = N-back test of working memory 0-back condition.

1-Back Condition = N-back test of working memory 1-back condition.

2-Back Condition = N- back test of working memory 2-back condition.

* $p < .05$, one-tailed for composite domain comparisons.

** $p < .05$, one-tailed after adjustment for multiple comparisons for test scores.

Table 9

Results of non-parametric correlations between the declarative memory composite score and the continuous medical and demographic variables for participants in the chronic steroid group

Variable	DECOM	Significance (<i>p</i>)
Age (months)	.25	.34
Education (years)	.03	.91
WRAT-3 reading	.33	.20
Systolic Blood Pressure (mm Hg)	-.17	.52
Diastolic Blood Pressure (mm Hg)	.22	.40
MMF dose per day (mg)	.17	.51
Duration of Dialysis (months)	-.44	.07
Months since Transplant	.48	.05
GFR (ml/min/1.73m ²)	.10	.72
BSI (GSI)	-.33	.21
Tacrolimus dose per day (mg)	-.40	.14

Note. DECOM = Declarative memory Composite Score.

Coefficients under DECOM represent values of Spearman's rho.

WRAT-3 reading = Wide Range Achievement test 3rd Edition, reading subtest raw score.

BSI (GSI) = Brief Symptom Inventory (General Severity Index) raw score.

Mm Hg = Millimeters of mercury.

MMF = mycophenolate mofetil.

**p* < .05.

Table 10

Kendall tau correlations between the categorical demographic and medical variables and the declarative memory composite score for participants in the chronic steroid group

Variable	DECOM	Significance (<i>p</i>)
Gender	.28	.18
African Americans	-.07	.75
European Americans	.10	.65
Hypertensives	.16	.43
Cadaveric Transplants	.34	.06
Hemodialysis	-.13	.53

Note. *N* = 17.

DECOM = Declarative memory composite score.

Values under DECOM are values of Kendall's *T*.

**p* < .05.

Table 11

Spearman's correlations and the corresponding values of eta-squared between the continuous medical and demographic variables and dose of prednisone for participants in the chronic steroid group

Variable	$r_s (\eta^2)$	Significance (p)
Age (months)	.26 (.08)	.32 (.54)
Education (years)	.15 (.06)	.57 (.65)
WRAT-3 reading	-.07 (.09)	.79 (.52)
Systolic Blood Pressure (mm Hg)	-.04 (.02)	.87 (.88)
Diastolic Blood Pressure (mm Hg)	-.39 (.23)	.13 (.16)
MMF dose per day (mg)	-.08 (.01)	.78 (.92)
Duration of Dialysis (months)	.22 (.22)	.41 (.18)
Months since Transplant	-.62 (.34)	.01 (.06)
GFR (ml/min/1.73m ²)	-.22 (.09)	.41 (.51)
BSI (GSI)	-.02 (.06)	.94 (.66)
tacrolimus dose per day (mg)	.20 (.08)	.50 (.34)

Note. $N= 16$ for r_s and $N= 17$ for eta-squared.

Significance values in parentheses represent tests of the significance of eta-squared.

MMF = mycophenolate mofetil.

WRAT-3 reading = Wide Range Achievement test- 3rd Edition, reading subtest raw score.

BSI (GSI) = Brief Symptom Inventory (General Severity Index) raw score.

* $p < .05$ after adjustment for multiple correlations.

Table 12

Summary of Standard Regression Analysis of declarative memory on duration of dialysis for participants in the chronic steroid group ($N = 16$).

Variable	B	SE B	β	Significance
Dialysis Duration	-.41	.19	-.49	.04*

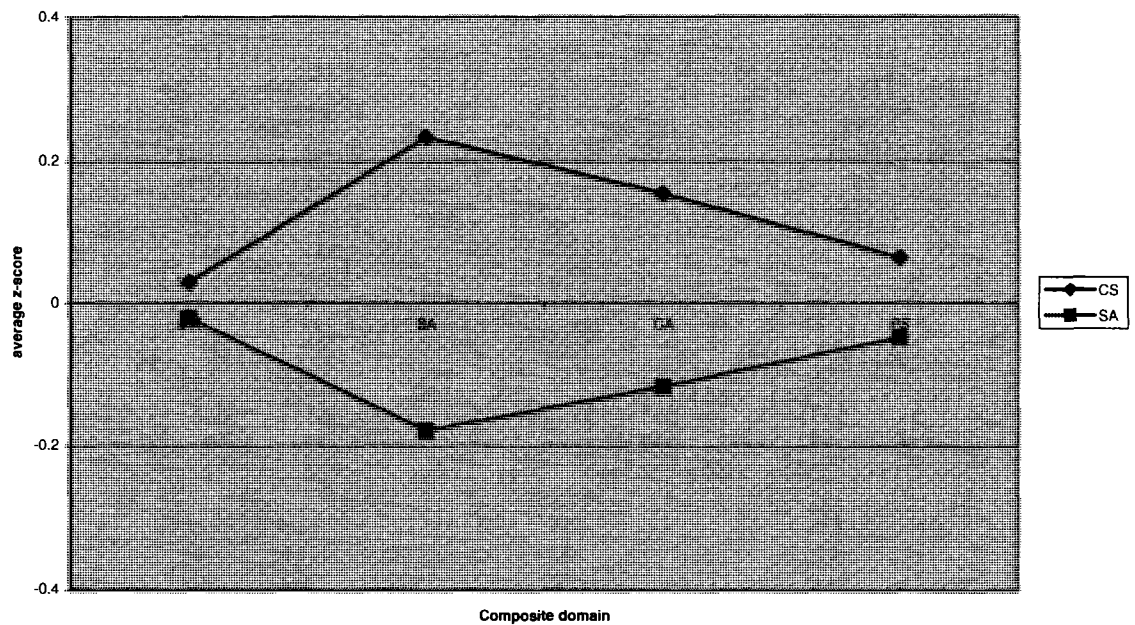
Note. * $p < .05$.

$R^2 = .24$.

Adjusted $R^2 = .19$.

Figure Caption

Figure 1. Mean z-scores for each of the four cognitive composite domains for participants in the Chronic Steroid (CS) and Steroid Avoidance Groups (SA).



Note. DM= Declarative memory composite score.

SA= Simple attention composite score.

CS= Complex attention composite score.

PS= Processing speed composite score.

Figure Caption

Figure 2. Scatterplot of the non-linear relationship between the declarative memory composite score (y-axis) and the mean dose of prednisone (x-axis) with the inclusion of the 7.5 mg data point for participants in the Chronic Steroid Group.

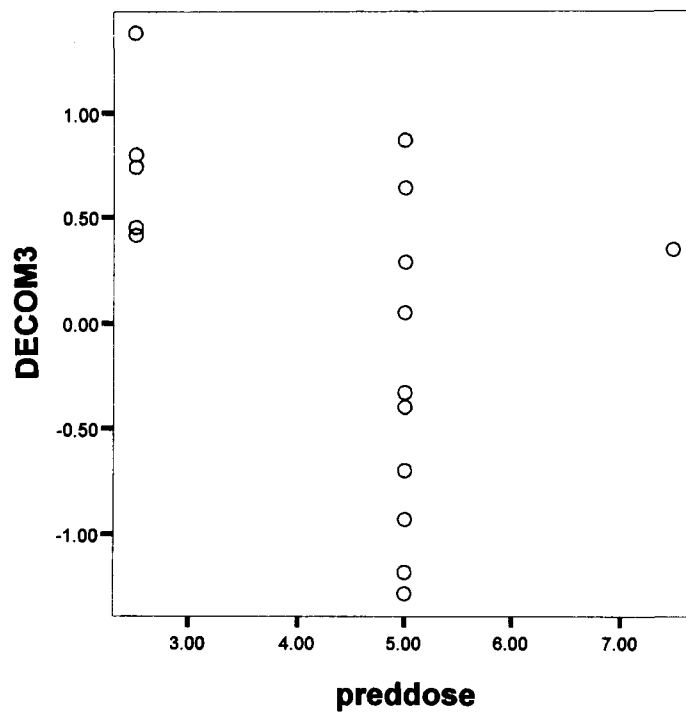
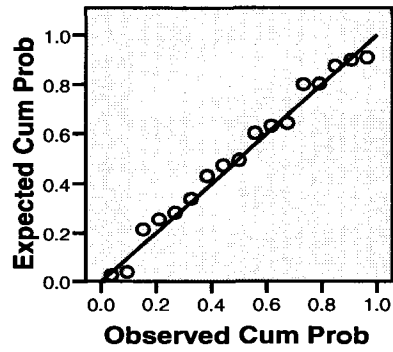


Figure Caption

Figure 3. Normal probability plot and scatterplot of the standardized residuals for the regression of duration of dialysis prior to transplant on the declarative memory composite score.

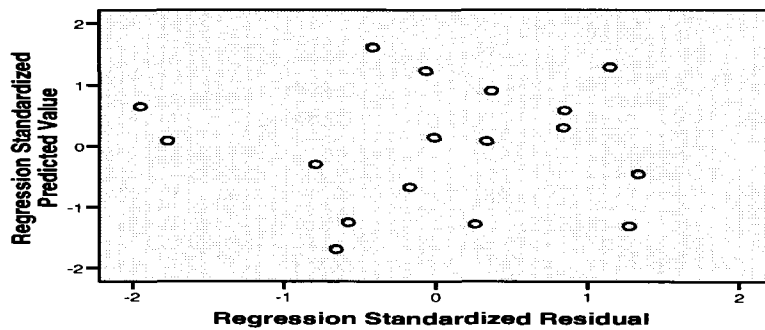
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: DECOM3



Scatterplot

Dependent Variable: DECOM3



Note. DECOM3= Declarative memory composite score.

APPENDIX A

List of Common Abbreviations

CKD- Chronic Kidney Disease

HD- Hemodialysis

PD- Peritoneal Dialysis

GFR- Glomerular Filtration Rate

Bsa- Body Surface Area

Kt- Total cleared volume of urea

V- Distribution Volume

t- Total dialysis time

CAPD- Continuous Ambulatory Peritoneal Dialysis

TMTA- Trail Making Test Part A

TMTB- Trail Making Test Part B

WAIS-R- Wechsler Adult Intelligence Scale- Revised

WMS- Wechsler Memory Scale

PASAT- Paced Auditory Serial Addition Test

WMS-III- Wechsler Memory Scale- 3rd Edition

WAIS-III- Wechsler Adult Intelligence Scale- 3rd Edition

SAM- Sympathetic-Adrenal-Medullary axis

HPA- Hypothalamic-Pituitary-Adrenal-Cortical system

MC- Mineralocorticoid

GC- Glucocorticoid

MR- Mineralocorticoid Receptor

GR- Glucocorticoid Receptor

CORT- Corticosterone

ADX- Adrenalectomized

ACTH- Adrenocorticotrophic hormone

PSE- Positive Slope Elevated

PSM- Positive Slope Moderate

NS- Negative Slope

WCST- Wisconsin Card Sorting Test

WMS-R- Wechsler Memory Scale- Revised

MRI- Magnetic Resonance Imaging

RAVLT- Rey Auditory Verbal Learning Test

LMI- Logical Memory I

LMII- Logical Memory II

APPENDIX B

Research Informed Consent Form

Title of Study: The Effect of Chronic Low-dose Prednisone on Neuropsychological functioning in Renal transplant Recipients

You are being asked to be in a research study of the effects of Prednisone therapy on memory and thinking at Wayne State University. Please read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Steven F. McArthur, Ph.D., Department of Psychiatry, Wayne State University in conjunction with Nikhil S. Koushik, M.A., Doctoral Candidate, University of Windsor and Anne D. Baird, Ph.D., Associate Professor, University of Windsor.

Study Purpose:

The purpose of the study is to find out if long-term Prednisone exposure causes problems with memory and thinking. The estimated number of study participants to be enrolled at Wayne State University is about 42.

Study Procedures:

If you take part in the study, you will be asked to take part in a variety of paper and pencil based tasks.

- These tasks will consist of a survey relating to current mental health functioning as well as measures of memory and problem solving.
- To be included in the study you will have to answer all the questions on the survey of mental health functioning. Other information that will be gathered includes: years of education and handedness.
- You may be asked some questions that make you uncomfortable. You may choose not to answer those specific questions and still participate in the study.
- The study will require approximately 2 hours of your involvement and, if possible, will be coordinated with your regular clinic appointment.
- If you complete all the necessary testing you will receive a one-page summary of your performance at your next clinic appointment. The group results for the study, but with **absolutely no** identifying information, will be posted on the University of Windsor ethics website at:
<http://web4.uwindsor.ca/units/researchEthicsBoard/studyresultforms.nsf/VisitorView?OpenForm>
- These results will be posted latest by January 31, 2008.

Benefits:

- The possible benefits to you for taking part in this study are that you will learn whether you have significant problems with memory or other areas of thinking. If such a problem is revealed you will receive the appropriate referral for treatment through your transplant nephrologist. Also, by taking part in this study you will help your transplant nephrologist better manage your care. Information from this study

may also reveal that long-term exposure to steroids may result in problems with memory and problem solving for transplant recipients in general. Furthermore, the data you provide with regard to memory and problem solving may be used in subsequent investigations to better understand the long-term impact of Prednisone therapy.

Risks: There are no known risks at this time to participation in this study.

Compensation:

- For taking part in this research study, you will be paid twenty dollars (\$20.00) for your time and inconvenience.
- If you consent to be enrolled in the study, you will then be administered a few small paper-and-pencil tasks to further demonstrate your eligibility. These tasks will not take more than 15 minutes.
- These few tasks will be scored by the test administrator on the spot. If your performance on these measures falls within the specified limits then the rest of the tasks will be administered and you will be paid twenty dollars (\$20.00).
- **BUT**, if your performance on these tasks does not fall within the specified limits, the administrator will explain the reason for your exclusion and you will be paid ten dollars (\$10.00). In this case the rest of the tests will not be administered, and you will be free to leave.

Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. You will be identified in the research records by a code name or number. Information that identifies you personally will not be released without your written permission. However, the study sponsor, the Human Investigation Committee (HIC) at Wayne State University or federal agencies with appropriate regulatory oversight, may review your records.

Personal Health Information (PHI) used and disclosed for the purposes of this study is protected under the federal regulation known as HIPAA (Health Insurance Portability and Accountability Act). Your study investigator will discuss with you your rights under this federal regulation and obtain your authorization to allow the research team to access your PHI.

Voluntary Participation /Withdrawal:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part, you can change your mind later and withdraw from the study. You are free to not answer any questions or withdraw at any time. Your decision will not change any present or future relationships with Wayne State University or its affiliates or other services you are entitled to receive. Your decision to withdraw from the study will not affect your health care or treatment in the Renal Transplantation Program in any way. If you choose to withdraw from the study you will **not** receive any monetary compensation. The investigator, or the sponsor, may stop your participation in this study without your consent. While taking part in this study, you will be told of any important new findings that may change your willingness to continue to take part.

Questions:

If you have any questions now or in the future, you may contact Steven F. McArthur, Ph.D., or one of his/her research team members at the following phone number. If you have questions or concerns about your rights as a research participant, the Chair of the Human Investigation Committee can be contacted at (313) 577-1628.

Consent to Participate in a Research Study:

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

Signature of Participant / Legally Authorized Representative Date

Printed Name of Participant/ Authorized Representative Time

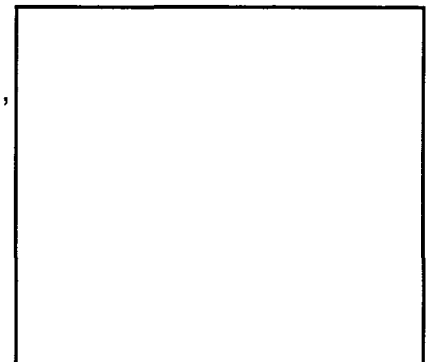
**Signature of Witness (When applicable) Date

Printed Name of Witness Time

Signature of Person Obtaining Consent Date

Printed Name of Person Obtaining Consent Time

** Use when participant has had consent form read to them (i.e., translated into foreign language).



APPENDIX C

List of Additional Questions pertaining to Symptoms of Psychological Disturbance

1. Have you had any thoughts of suicide or harming yourself in the past two weeks?
2. Do you hear or see things other people don't?
3. Do you still take pleasure in activities you find interesting?
4. Have you noticed a significant (i.e., >5%) change in your body weight in the last two weeks?
5. Do you have crying spells for no apparent reason (i.e., find yourself crying but don't know why)?
6. Have you been feeling more sad than usual over the last two weeks?
7. Have you noticed a decrease (e.g., sleep only about 3 hours and feel rested) in your need for sleep in the last week?
8. Have you felt more restless or on-edge in the past 6 months?
9. Have you felt like your thoughts were racing faster than you could get them out in the past week?
10. Have you taken on any large projects (i.e., painting the house, tiling the kitchen) in the past week and worked on them endlessly without feeling very hungry or tired?
11. Have you recently noticed times when your heart was racing or pounding for no apparent reason?
12. Have you recently experienced periods of excessive sweating for no reason?
13. Have you recently experienced periods of excessive shaking or trembling for no apparent reason?
14. Have you recently experienced any physical symptoms such as nausea, pain in your chest, shortness of breath, light-headed or dizziness for no apparent reason?
15. Do you ever have thoughts, not just about real-life problems, that you just can't seem to get out of your head?
16. Do these thoughts cause you to worry excessively?

17. Have you had difficulty falling or staying asleep in the past two weeks because you very tense or worried?
18. Are there any behaviours you do regularly (>4 times/day), for example, washing your hands or checking to make sure the stove is turned off?
19. Have you noticed you have been more physically tense in the last 6 months?
20. Have you noticed you have been more irritable than usual in the last 6 months?
21. Have you noticed a drastic increase in the amount you sleep in the last 2 weeks?
22. Have you found it difficult to concentrate on things you had to do in the last 2 weeks?
23. Have you felt a significant loss of energy in the past two weeks?

Decision Rules

Discontinue if the patient answers “yes” to items 1 or 2.

Discontinue if the patient answers “yes” to at least five of items 3, 4, 5, 6, 21, 22, and 23.

Discontinue if the patient answers “yes” to at least two of items 7, 9, and 10.

Discontinue if the patient answers “yes” to at least two of items 11, 12, 13, and 14.

Discontinue if the patient answers “yes” to at least two of items 15, 16, and 18.

Discontinue if the patient answers “yes” to at least three of items 8, 17, 19, 20, 22, or 23.

APPENDIX D

Standard psychometric properties of tests used in the battery

Test	Internal Reliability	Test Re-test Reliability	Internal Validity	Convergent Validity
RAVLT				
Total 1-5	.90	.77		.82
Delayed Recall			.75	.75
Recognition				.60
WAIS-III				
Digit Span	.90		.83	.82
Letter-Number Sequencing	.82		.85	
Coding		.84	.91	.77
Symbol Search		.77	.91	.67
WMS-III				
Logical Memory I	.88		.85 (.48)	
Logical Memory II	.79		.85 (.46)	
Spatial Span	.79		.45	
TMT Part A		.79	.31-.36	.33
TMT Part B		.89	.31-.36	.60

Stroop Dot	.90	.17-.56
Stroop Word	.83	.17-.56
Stroop Interference	.91	.17-.56

Note. Sources of the information in this appendix are listed in Appendix E.

For Coding, Symbol Search, TMTA, TMTB, and Stroop Dots, Words and Interference only

test-retest reliabilities are reported due to the timed nature of these tests.

Numbers in parentheses represent the intercorrelations between Logical Memory I and II scores and Verbal Paired Associate I and II scores respectively.

RAVLT = Rey Auditory Verbal Learning Test

Total 1-5 = Total words recalled trials 1-5.

WAIS-III = Wechsler Adult Intelligence Scale, 3rd Edition.

WMS-III = Wechsler Memory Scale, 3rd Edition.

TMT Part A = Trail Making Test Part A time to completion.

TMT Part B = Trail Making Test Part B time to completion.

Stroop Dot = Stroop Dots trial time to completion.

Stroop Word = Stroop Words trial time to completion.

Stroop Interference = Stroop Colour-Word trial time to completion.

APPENDIX E
Published sources of psychometric data for tests used in the battery

Test	Internal Reliability	Test Re-test Reliability	Internal Validity	Convergent Validity
RAVLT	Van den Burg & Kingma (as cited in Strauss, Sherman, & Spreen, 2006)	Ryan et al. (as cited in Schmidt, 1996)	Intercorrelation with total words recalled Van den Burg Kingma (as cited in Strauss, Sherman, & Spreen, 2006)	Criterion is the WMS-III Logical Memory subtest. Malec et al. (as cited in Schmidt, 1996)
Total 1-5				
Delayed				
Recall				
Recognition				
WAIS-III	Wechsler (1997)	Wechsler (1997)	Intercorrelation with other subtests within the respective factor (Wechsler, 1997).	Criterion is the WAIS-R for all subtests but is the WISC-III for Symbol Search (Wechsler, 1997).
Digit Span				
Letter-				
Number Sequencing				
Coding				
Symbol				
Search				

WMS-III	Wechsler (1997)	Intercorrelation between logical memory I and II subtests (Wechsler, 1997).	
Logical Memory			
Spatial Span TMT Part A	Dikmen et al. (as cited in Strauss, Sherman, & Spreen, 2006)	Intercorrelations with each other. Royan et al. (as cited in Strauss, Sherman, & Spreen, 2006)	Criterion is the Paced Auditory Serial Attention Test. Royan et al. (as cited in Strauss, Sherman, & Spreen, 2006)
TMT Part B			
Stroop Dot	Bullock et al. (unpublished data) (as cited in Strauss, Sherman, & Spreen, 2006)	Intercorrelation ranges between the three subtests of the Stroop. Pineda et al. (as cited in Strauss, Sherman, & Spreen, 2006)	Criterion is number of trials to completion on the Tower of London Test. Hanes et al. (as cited in Strauss, Sherman, & Spreen, 2006)
Stroop Word			
Stroop Interference			

Note. RAVLT = Rey Auditory Verbal Learning Test.

Total 1-5 = Total words recalled trials 1-5.

WAIS-III = Wechsler Adult Intelligence Scale, 3rd Edition.

WAIS-R = Wechsler Adult Intelligence Scale, Revised.

WISC-III = Wechsler Intelligence Scale for Children, 3rd Edition.

WMS-III = Wechsler Memory Scale, 3rd Edition

TMT Part A = Trail Making Test Part A.

TMT Part B= Trail Making Test Part B.

Vita Auctoris

Nikhil Koushik is a graduate student in neuropsychology nearing the completion of his training at the University of Windsor. Current research interests include classification issues in childhood diseases, chronic kidney disease, and the relationship between medical variables and neurocognition.