ATTENTION FUNCTIONS IN CHILDREN WITH PEDIATRIC CHRONIC KIDNEY DISEASE

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ABSTRACT

Peter Duquette: Attention Functions in Children with Pediatric Chronic Kidney Disease
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Children with chronic kidney disease (CKD) can evidence a variety of general and specific neurocognitive deficits, but little is known regarding the effects of pediatric CKD on specific domains of attention. Using a variety of measures tapping specific domains (e.g., Focus/Execute, Sustain, Stability, Shift, Encode), the current study compared attention outcomes for school-age children with CKD to those of a typically-developing control group.

The study addressed the following research questions: 1) Do specific domains of attention in children and adolescents with CKD differ significantly from those measured in typically-developing children and adolescents? 2) Do pediatric patients with CKD differ significantly from typically-developing children in their observed proportion of attention problems? 3) What functional- (e.g., recent school absences, IQ), family- (e.g., socioeconomic status), and disease-related (e.g., disease severity, age of onset, duration of disease) characteristics predict attention domain scores?

Significant differences on group means were revealed between the CKD (n = 30) and control (n = 41) groups on the Focus/Execute, Sustain, Stability, and Encode attention domains; no group differences were evident on the Shift domain. The CKD group also had a larger proportion of children with attention domain scores one standard deviation or more below the mean on the Shift and Encode domains. The CKD and

control groups did not differ with respect to the proportion of scores falling one standard deviation or more below the mean on the Focus/Execute, Sustain, or Shift domains. Correlational data indicated that IQ scores and socioeconomic status were positively correlated with all five attention domains, while disease severity was negatively correlated with the attention domains. Exploratory regression analyses indicated that IQ scores were a significant predictor of the Stability and Encode attention domains. No predictors emerged for the Focus/Execute, Sustain, or Shift attention domains.

In exploratory analyses with a subdivided CKD group, the end-stage renal disease (ESRD, i.e., kidney failure) group was found to have a higher proportion of attention scores one standard deviation or more below the mean on the Focus/Execute, Sustain, and Stability domains. Exploratory univariate comparisons of children with ESRD versus those with mild/moderate CKD further suggested a potential effect of disease severity on attention.

Findings suggested that children with CKD may be vulnerable to subtle, specific deficits in domains of attention relative to their typically-developing peers. Results also suggested that this finding of specific attention problems may be particularly relevant for children with more severe levels of CKD. Facets of the current study, such as small sample size and other limitations, precluded broad generalizations of these findings to the pediatric CKD population as a whole. Future research should utilize regression analyses to develop a model of risk using predictor variables when screening for neurocognitive deficits. Using larger sample sizes and longitudinal analyses in future research may help to distinguish subtle attention problems in this population. Limitations and suggestions for future research are discussed.

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ABBREVIATIONS

ACPT	Keith Auditory Continuous Performance Test
CKD	Chronic Kidney Disease
CPT	Continuous Performance Test
CRI	Chronic Renal Insufficiency
EF	Executive Function
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FSGS	Focal Segmental Glomerulosclerosis
GDS	Gordon Diagnostic System
IQ	Intelligence Quotient
KDOQI	Kidney Disease Outcomes Quality Initiative
NKF	National Kidney Foundation
RFFT	Ruff Figural Fluency Test
SES	Socioeconomic Status
TOL	Tower of London, Second (Drexel University) Edition
WASI	Wechsler Abbreviated Scale of Intelligence
WRAML	Wide Range Assessment of Memory and Learning

CHAPTER I

INTRODUCTION

Overview

Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive deterioration of kidney function that cannot be reversed, and ultimately hinders the body's ability to eliminate harmful toxins and waste products. Criteria for CKD encompasses kidney function below approximately 75% of normal, and extends down to include individuals with little to no native function who are dependent on dialysis or a kidney transplant. The National Kidney Foundation (NKF) through the Kidney Disease Outcomes Quality Initiative (KDOQI; NKF, 2002) has set forth guidelines that classify CKD into five stages of severity based on a measure called the estimated glomerular filtration rate (eGFR) as calculated by the Schwartz formula (Schwartz, Haycock, Edelmann, & Spitzer, 1976). This calculation provides an estimate of CKD severity based on how well an individual's kidneys are filtering waste products within the body. KDOQI represents an effort to improve patient outcomes through the development of clinical practice guidelines, by defining CKD according to the presence or absence of markers of kidney damage and the level of kidney function (eGFR), irrespective of the type of kidney disease or specific diagnosis. The two independent criteria for CKD include the following: 1) Kidney damage for at least 3 months as defined by structural or functional abnormalities of the kidney, with or without decreased eGFR, manifested through either pathological

abnormalities or markers of kidney damage (e.g., blood or urine composition abnormalities, or abnormalities found in imaging tests); or 2) An eGFR less than 60 mL/min/1.73m2 for at least 3 months, with or without kidney damage.

An individual's eGFR is the most informative index of kidney function in terms of health and disease. Normal ranges for eGFR vary based on age, sex, body size, and serum creatinine levels in the blood. Among individuals with CKD, the stage of severity is defined based on the level of kidney function using eGFR, with the higher CKD stages representing lower GFR levels (see Table 1).

Table 1.

KDOQI guidelines for stages of CKD.

Stage	Description	eGFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	$\geq$ 90
2	Kidney damage with mild decrease in GFR	60 – 89
3	Moderate decrease in GFR	30 – 59
4	Severe decrease in GFR	15 – 29
5	Kidney failure	< 15 (or dialysis)

Stage 1 of CKD represents patients with kidney damage who have normal or elevated eGFR levels ($\geq$ 90 mL/min/1.73m^2). Stages 2-4 correspond to patients with CKD who are treated with conservative therapies, and are often referred to as having chronic renal insufficiency (CRI). Stage 2 includes patients with kidney damage and a mild decrease in eGFR levels (60-89 mL/min/1.73m^2). Stage 3 includes patients with kidney damage and a moderate decrease in eGFR levels (30-59 mL/min/1.73m^2), while Stage 4 includes patients with kidney damage and severe/significant decreases in eGFR

level (15-29 mL/min/1.73m^2). Patients with end-stage renal disease (ESRD) encompass Stage 5 of CKD, which is defined as dialysis or transplant dependence or an estimated glomerular filtration rate (eGFR) $\leq$ 15 mL/min/1.73m^2.

The term CKD is used to describe the full spectrum of kidney dysfunction, including individuals with CRI (also referred to as mild, moderate, or severe CKD) and ESRD (also referred to as kidney failure). In contrast to adults, for whom the main causes of CKD are diabetes and high blood pressure, the most common causes of CKD in children are congenital abnormalities, including obstructive uropathy, renal dysplasia, reflux nephropathy, and focal segmental glomerulosclerosis (NKF, 2002; U.S. Renal Data System, 2005).

CKD is a major public health problem, with a prevalence rate of ESRD in the United States of about 82.2 per million for individuals age birth to 19 years, and has been linked to poor health outcomes and high medical expenditures (U.S. Renal Data System, 2005). Recent improvements in dialysis regimens, transplantation procedures, nutritional support, and pharmacological management of comorbid anemia and hypertension have increased the survival rate for children with CKD to over 95% annually (Ferris, Gipson, Kimmel, & Eggers, 2006; Gipson, Wetherington, Duquette, & Hooper, 2004; Neu, Ho, McDonald, & Warady, 2002; Seikaly, Ho, Emmett, Fine, & Tejani, 2003; Smith, Ho, & McDonald, 2002; U.S. Renal Data System, 2005). Despite documented improvements in medical care and increased rates of patient survival in pediatric CKD, however, the literature continues to identify neurodevelopmental concerns in children associated with this chronic illness, particularly for children who progress to ESRD and are dialysis- or transplant-dependent (Bawden et al., 2004; Brouhard et al., 2000; Crocker et al., 2002;

Davis, Chang, & Nevins, 1990; Duquette, Hooper, Wetherington, Jenkins, & Gipson, 2007; Elzouki, Carroll, Butinar, & Moosa, 1994; Fennell, Fennell, Carter, Mings, & Klausner, 1990a; Fennell et al., 1990b; Gipson, Wetherington, Duquette, & Hooper, 2004; Gipson et al., 2006; Groothoff, 2005; Hulstijn-Dirkmaat, Damhuis, Jetten, Koster, & Schroder, 1995; Lawry, Brouhard, & Cunningham, 1994; Ledermann et al., 2000; Mendley & Zelko, 1999; Qvist et al., 2002; Slickers, Duquette, Hooper, & Gipson, 2007; Warady, Belden, & Kohaut, 1999).

Previous Research

Neurodevelopment in Infants with CKD

Early research in the field heightened concerns regarding neurodevelopmental delays for infants and preschool children with CKD (McGraw & Haka-Ikse, 1985; Polinsky, Kaiser, Stover, Frankenfield, & Baluarte, 1987; Rotundo et al., 1982; Warady, 2002). This literature indicated rather poor developmental outcomes for children with CKD during infancy, with the incidence of developmental delays estimated between 60-85% (Bale, Siegler, & Bray, 1980; Baluarte, Gruskin, Hiner, Foley, & Grover, 1977; Bird & Semmler, 1986; Bock et al., 1989; McGraw & Haka-Ikse, 1985; Polinsky et al., 1987; Rotundo et al., 1982; So et al., 1987, Warady, 2002). Developmental delays in infants and preschool children with CKD have been linked to a number of negative outcomes in the literature, including neurological conditions (e.g., microcephaly, seizures), mental retardation, reduced growth rates, impaired hemispheric maturation, and abnormal electrophysiological findings (Bock et al., 1989; Kari, Gonzalez, Ledermann, Shaw, & Rees, 2000; McGraw & Haka-Ikse, 1985; Polinsky et al., 1987; Rotundo et al., 1982; So et al., 1987; Van Dyck & Proesmans, 2001).

More recent research has suggested that severe neurodevelopmental problems may be less common than previously estimated for infants and preschool children with CKD (Duquette et al., in press; Elzouki et al., 1994; Geary & Haka-Ikse, 1989; Madden, Ledermann, Guerrero-Blanco, Bruce, & Trompeter, 2003; Warady, 2002; Warady et al., 1999). Current estimates suggest that neurodevelopmental delays, broadly defined, are evident in approximately one-fourth of young children with CKD (Gipson et al., 2004). The increase in positive findings outcomes reported in the literature with regards to early neurodevelopment in CKD has been correlated with several recent trends in treatment, including use of transplantation at earlier ages, increased protein and caloric intake through advanced nutritional support, and the elimination of aluminum-containing phosphate binders and improved water purification during dialysis (Elzouki et al., 1994; Geary & Haka-Ikse, 1989; Ledermann et al., 2000; NKF, 2001; Qvist et al., 2002; Warady, 2002; Warady et al., 1999).

Neurocognition in School-Age Children with CKD

For older children with CKD, more formal measures of intelligence (IQ) have been obtained, with the general consensus being that school-age children with CKD show a normal distribution of IQ scores that is shifted slightly downward compared with the normal population (Bawden et al., 2004; Brouhard et al., 2000; Duquette et al., 2007; Gipson et al., 2006; Hulstijn-Dirkmaat et al., 1995; Lawry et al., 1994; Madden et al., 2003; Mendley & Zelko, 1999; Qvist et al., 2002). Cross-sectional case-control studies on children with CKD have reflected this trend. Brouhard and colleagues (2000) reported significantly lower IQ scores for children with ESRD, including both dialysis and transplant groups, when compared to a sibling control group. Bawden and colleagues

(2004) also found significant differences in IQ between children with ESRD versus a typically-developing, matched control group, with children in the ESRD group having lower Verbal IQ, Performance IQ, and Full Scale IQ scores. Warady and colleagues (1999) also reported that that 21% of their sample of school-age children with ESRD from infancy had Full Scale IQ scores below the average range (i.e., defined as age-based Standard Scores 90 – 109). Among this sample, only 72% of participants achieved at least average Verbal IQ scores, while only 56% had average Nonverbal IQ scores (Warady et al., 1999).

Comparisons of Full Scale IQ scores within groups of children with CKD have produced variable results. Lawry and colleagues (1994) evaluated transplanted children (n = 13) and dialysis-dependent children (n = 11) in a cross-sectional study, and found a higher mean IQ in the transplant group, although both groups fell largely within the average range. Similarly, Crocker and colleagues (2002) found no differences between children with ESRD from birth (congenital) versus children with acquired ESRD. Conversely, in a cross-sectional study, no differences were reported for the intellectual functioning of transplant versus dialysis-dependent groups (Brouhard et al., 2000).

Findings in the literature also point to significant concerns for the neuropsychological integrity of children with CKD across specific domains of functioning. Contemporary studies on attention, memory, and executive functions with pediatric CKD samples suggest that these areas of neurodevelopmental concern should be monitored continually over time (Fennell et al., 1990; Gipson et al., 2006; Mendley & Zelko, 1999; Qvist et al., 2002). Findings suggest the possibility that the progression of CKD may disrupt attention, memory, and executive functions beyond the generalized

effects of lower IQ and lower socioeconomic status (SES; Gipson et al., 2006). These neuropsychological deficits associated with CKD may subsequently impact a child's life course by limiting the degree of educational attainment and future vocational choices available to this population (Groothoff, 2005).

Factors Influencing Neurocognitive Problems in CKD

A number of factors have been proposed to explain the presence of neurocognitive dysfunction in the pediatric CKD population. The age of onset and duration of illness (Crocker et al., 2002; Davis et al., 1990; Elzouki et al., 1994; Hulstijn-Dirkmaat et al., 1995; Lawry et al., 1994; Madden et al., 2003), the modality of renal replacement therapy (Brouhard et al., 2000; Hulstijn-Dirkmaat et al., 1995; Qvist et al., 2002; Warady et al., 1999), and complications of CKD treatment including aluminum toxicity, malnutrition, anemia, and hypertension (Gorman, 1995; Grantham-McGregor, 1995; Halterman, Kaczorowski, Aligne, Auinger, & Szilagyi, 2001; Lande, Kaczorowski, Auinger, Schwartz, & Weitzman, 2003; Levitsky & Strupp, 1995; Marsh et al., 1991), all may contribute to these deficits.

Aluminum neurotoxicity is the presence of measurable amounts of aluminum in the brain resulting from increased aluminum levels in the blood and subsequent passage through the blood-brain barrier. For patients with CKD, aluminum levels were at one time elevated due to impure dialysis water purification during hemodialysis, in which the patient's blood is filtered through an external machine to remove toxins and waste products to provide clean blood to the body. Research into this treatment method, in addition to the use of aluminum-containing phosphate binders, established a clear connection with neurocognitive dysfunction (Andreoli, Bergstein, & Sherrard, 1984;

Sedman, Miller, Warady, Lum, & Alfrey, 1984; Sedman, Wilkening, Warady, Lum, & Alfrey, 1984). The neurocognitive effects of aluminum-induced neurotoxicity included seizures, speech disorders, dementia, and a slow pattern on EEG (Alfrey, LeGendre, & Kaehny, 1976; Andreoli et al., 1984). The effects of aluminum intoxication from long-term hemodialysis in adults with ESRD also were associated with severe cognitive deterioration and death (Alfrey, 1978; Lederman & Henry, 1978). This was a key finding for the field in that it encouraged modifications to the dialysis treatment regimen and highlighted a confounding factor in the relationship between CKD and neurocognitive integrity. By the 1990s, the use of improved dialysis water purification techniques and avoidance of aluminum-containing medications reduced the confounding factor of aluminum intoxication during treatment processes (Gipson et al., 2004), and is therefore no longer empirically relevant for contemporary studies of pediatric patients with CKD.

Malnutrition is another significant issue for patients with CKD that can potentially lead to neurocognitive deficits (Conley, 1987; NKF, 2001; Warady, 2002; Winick, 1969). Malnutrition is important for patients with CKD due to the need for low intake of protein, phosphorus, and sodium in this population because the kidneys do not filter these materials well with suboptimal function (NKF, 2001). Protein is converted in the body into a waste product called urea once it is fully consumed for muscle growth and tissue repair, and suboptimal function of the kidneys causes urea to build up in the body and leads to negative cognitive effects (Gipson et al., 2004). Furthermore, high levels of phosphorus in the body lead to decreased calcium levels and cause bones to break more easily (NKF, 2001). Efforts to control kidney function through dietary restrictions can lead to malnutrition if patients do not receive adequate levels of necessary minerals and

vitamins over an extended period of time; however, most inter-disciplinary teams that treat children with CKD include nutritionists for this exact reason (NKF, 2001). In this sense, malnutrition, much like aluminum neurotoxicity, also poses less of a threat currently to neurocognitive function in the CKD population due to improvements in treating this co-occurring aspect of CKD. Generally speaking, the impact of malnutrition on cognitive function has been well-documented broadly in the literature (Grantham-McGregor, 1995), with evidence of generalized cognitive deficits manifested as low IQ scores, academic underachievement, and increased behavioral problems. These issues persist into adolescence, but do improve significantly with appropriate interventions, although the exact mechanism linking malnutrition to neurocognitive deficits has not been established to this point (Grantham-McGregor, 1995).

Anemia and hypertension are issues that continue to this day to have important implications for neurocognitive function in children with CKD. Low red blood cell counts and decreased hemoglobin levels have been extensively associated with neurocognitive dysfunction in the pediatric sickle cell disease population (Kral, Brown, & Hynd, 2001; Lemanek, Ranalli, Green, Biega, & Lupia, 2003; Noll et al., 2001). It serves to reason then that anemia secondary to CKD could also affect neurocognitive function, and the literature has backed this claim. Erythropoietin (also referred to as epogen and EPO) was introduced into standard practice in the early 1990s, resulting in improved anemia management in the CKD population (Gipson et al., 2004). In adults with ESRD, a diminution of anemia-related EEG abnormalities and cognitive deficits were subsequently reported (Marsh et al., 1991; Pickett, Theberge, Brown, Schweitzer, & Nissenson, 1999; Sagales, Gimeno, Planella, Raguer, & Bartolome, 1993).

Similar concerns are evident with regards to neurocognitive function and hypertension. In addition to the wealth of literature suggesting neurocognitive dysfunction in elderly individuals with hypertension, a population-based study of children with hypertension has shown that these children have difficulties with tasks requiring memory, attention, and concentration (Lande et al., 2003). For patients with hypertension and CKD, additional dietary concerns specific to the need for low sodium intake presents another challenge to these individuals.

Current Study

The current study examined attention in children and adolescents with chronic kidney disease (CKD) relative to a group of typically-developing peers. Data were examined from an existing database collected on a sample of children in North Carolina who received medical treatment for CKD at a local university teaching hospital, and a comparison group that was recruited from within the catchment area of that same hospital. Data included outcome measures tapping into components of attention obtained via standardized neuropsychological testing administered by a trained examiner under the supervision of a clinical neuropsychologist. Demographic and other related variables collected via informal questionnaire were also examined.

Statement of Purpose

Attention is a key component of developmental success in the academic, vocational, and interpersonal domains. Problems with lack of sustained focus, inconsistent concentration, limited storage of working memory, and/or lack of inhibitory controls can potentially have negative impacts on multiple areas of functioning. Furthermore, such problems can persist throughout childhood and adolescence and into

adulthood, thereby increasing the likelihood that related problems could occur. For these reasons, and given the research suggesting that CKD may lead to negative neurocognitive outcomes during childhood and adolescence, it is important that the specific domains of attention of pediatric patients with CKD be examined carefully.

The current study sought to add valuable information to an area where previous research is lacking. By investigating the integrity of attention in children with CKD in relation to their typically-developing peers, it was expected that critical information would be gained regarding the psychoeducational and treatment needs of this patient sample. With regard to specific neuropsychological domains, documented problems with attention have been associated with the degree to which children with CKD retrieve acquired information and build upon areas of hierarchical learning (Fennell et al., 1990b; Qvist et al., 2002). These studies have been conducted in a broader examination of the entire spectrum of neurocognitive functions, without using an a priori model underlying the conceptualization of attention. Understanding the integrity of specific attention domains in these patients could benefit the CKD population as a whole by increasing awareness for the need of psychoeducational support services if CKD is found to negatively impact attention and academic performance in children (Duquette et al., 2007), while also intervening at earlier time points to lessen the morbidity for medical, educational and future employment outcomes (Groothoff, 2005).

Research Questions and Hypotheses

Although recent medical advancements have resulted in increased survival rates for children with CKD, concerns related to neurodevelopmental outcomes persist for this pediatric population. To date, no studies have specifically examined attention in children

with CKD using a research-based neuropsychological model of attention, and only a handful of studies have examined executive functions in children with CKD. Using the neuropsychological model of attention pioneered by Mirsky and colleagues (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999) as an underlying basis, this study compared specific attention domains of children with CKD to those of a matched control group using a cross-sectional retrospective case-control design. This study addresses the following research questions and hypotheses:

1) Do specific domains of attention in children and adolescents with CKD differ significantly from those measured in typically-developing children and adolescents? Children with CKD may exhibit attention problems when compared to a matched control group. Taking the previous literature to date into consideration (Fennell et al., 1990a, 1990b; Gipson et al., 2006; Qvist et al., 2002; Yount, Jacobs, Bustamante, & Brickman, 1998) in the context of Mirsky's model of attention (1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999), it was hypothesized that the CKD group would score lower than the control group on several specific attention domains (Focus/Execute, Sustain, and Encode). It was also hypothesized that the CKD group would exhibit similar performance to the control group on several other attention domains (Stability, Shift).

2) Do pediatric patients with CKD differ significantly from typically-developing children in their observed proportion of attention problems? Specifically, does a higher proportion of pediatric patients with CKD evidence difficulties with attention one standard deviation or more below the mean (defined as an age-based Standard Score (SS)

≤ 85)? It was hypothesized that a higher proportion of children in the CKD group would demonstrate attention problems (SS ≤ 85) relative to the control group within several specific attention domains (Focus/Execute, Sustain, and Encode). It was also hypothesized that children in the CKD group would demonstrate similar proportions of problems on the Stability and Shift attention domains.

3) What functional- (e.g., recent school absences, IQ), family- (e.g., SES), and disease-related (e.g., disease severity, age of onset, duration of disease) variables predict attention domain scores? It was hypothesized that lower IQ scores, higher numbers of school absences, lower SES, earlier age of CKD onset, longer duration of CKD, more severe levels of CKD (lower eGFR calculations), and co-morbid diagnoses of anemia or hypertension would be associated with lower scores on all attention domains (Focus/Execute, Sustain, Stability, Shift, Encode). Furthermore, it was hypothesized that IQ scores, SES, and CKD severity (eGFR) would be significant predictors of all five attention domains within the proposed model of attention.

CHAPTER II

LITERATURE REVIEW

Introduction

Despite a number of studies examining the medical and neurodevelopmental outcomes related to chronic kidney disease (CKD), existing literature has not adequately addressed the integrity of attention in children and adolescents with CKD. Literature on attention functioning secondary to pediatric CKD reveals mixed findings (Fennell et al., 1990a, 1990b; Gipson et al., 2006; Mendley & Zelko, 1999; Qvist et al., 2002). Findings from this research are not consistent, and these studies do not utilize similar methodology or theoretical bases to examine attention in the pediatric CKD population.

To address the need for research evidence regarding the integrity of attention functioning in pediatric patients with CKD, the goals of the current study are to provide a basis to **1) compare performance within specific domains of attention in children and adolescents with CKD to that of a group of their healthy peers; 2) compare the frequency of attention dysfunction between these groups; and 3) determine what functional-, family-, and disease-specific variables are associated with and predict attention scores in children and adolescents with CKD.** The following chapter provides a review of recent literature and an empirically-based rationale for conducting the study. Topics covered include a review of previously investigated models of attention, attention outcomes in the CKD population, attention outcomes in other pediatric medical populations, and medical variables affecting neurocognitive processes.

Models of Attention

Problems with attention have been linked to a number of disorders and syndromes, including type 1 diabetes (Northam et al., 2001; Rovet & Alvarez, 1997), spina bifida (Dennis, Landry, Barnes, & Fletcher, 2006), sickle cell disease (Kral et al., 2001; Lemanek et al., 2003; Noll et al., 2001), pediatric HIV/AIDS (Armstrong, Willen, and Sorgen, 2003; Bisiacchi, Suppiej, & Laverda, 2000; Brouwers, Belman, & Epstein, 1994), pediatric cancer (Vannatta & Gerhardt, 2003), seizure disorder (Cohen, Malloy, & Jenkins, 1999), traumatic brain injury (Bigler, 2003), postnatal lead exposure (Chiodo, Jacobson, & Jacobson, 2004), post-traumatic stress disorder (Vasterling, Brailey, Constans, & Sutker, 1998), and congenital hypothyroidism (Rovet & Hepworth, 2001). However, the disorder most defined by significant attention problems is obviously attention-deficit/hyperactivity disorder (ADHD), with a prevalence rate estimated between 3-10% of school-age children nationwide (Barkley, 2003). The parents and teachers of children with attention problems face many frustrations which have given way to large commercial interests in this area over the last several decades, including numerous books, brochures, tools used to assess and treat these symptoms, and many pharmacological interventions. Scientific and theoretical contributions have been numerous, and are briefly reviewed next.

Multiple views on models of attention have been posited over the years, and variations among the models have been evident depending on the discipline supplying the research (e.g., psychiatry in clinical settings, research on cognitive processes, and neuropsychology) and over time. Early models viewed attention from the perspective of perceptual information processing (Broadbent, 1953; 1957) in which attention played the

role of a filtration system that attended to relevant information based on the intensity, importance, and novelty of the stimuli. Arousal theory is another model of attention popularized in the mid-20th century, which linked alertness to effortful function through the input of sensory stimuli (Pribram & McGuiness, 1975; Samuels, 1959). The incorporation of fluid cognitive abilities, such as concentration, flexibility, and processing speed (Stankov, 1988) has also been suggested to be salient in the discussion of attention. These early models provided important frameworks for conceptualizing attention as a multi-step or multi-component process, but empirically measuring the filtration of relevant information or degree of alertness under conditions that could be generalized to the real world became difficult. Additionally, the need to link specific brain regions to functional abilities also became increasingly important with the increased availability of neuroimaging and as cognitive neuroscience became more prevalent during the late 1970s and early 1980s.

Posner (Posner, 1980; Posner & Petersen, 1990) has posited a model of visual attention that utilizes approaches from cognitive neuroscience and described the process of orienting, shifting, and controlling one's attention. Posner contends that attention can be deployed in one of two ways during any visual search, either under the overt control of the individual (e.g., "top-down" or endogenous attention) or covertly without control of the individual (e.g., "bottom-up" exogenous attention). Endogenous attention is voluntary and effortful, whereas exogenous attention is rapid and automatically draws focus to a specific location. Stimulus-driven control of attention also involves interaction between the bottom-up and top-down attentional control systems in Posner's model (Posner, 1980). Inhibitory mechanisms and visual priming/cuing also play a significant

role in Posner's model with regards to shifting and returning attention to specific targets (Posner, 1980), with neural correlates being singled out in more recent examinations of the topic (Posner & Petersen, 1990). Although this model of visual attention is an important contribution to the field, it is problematic to entirely dismiss the impact of auditory input when conceptualizing domains of attention, which could be an area of specific weakness for the pediatric CKD population. Utilizing a model with expanded utility to include auditory vigilance and other attention subcomponents, such as stabilizing or encoding attention, could provide a comprehensive view.

More recently, attention has been closely associated with executive function (EF) constructs and neuropsychological functioning to formulate a multifaceted approach. EF constructs include such varied abilities as sustaining attention, controlling impulses, planning, organizing, maintaining a response set, and solving problems, with slight variations noted with each researcher (Cohen, 1993a, 1993b; Denckla, 1996). Executive control also taps into a specific component of EF dealing with self-regulation, self-direction, goal-directed behaviors, and response inhibition (Barkley, 2003; Cohen, 1993a, 1993b; Denckla, 1996). Various definitions of EF have been increasingly linked functionally to specific cortical structures and systems (Riccio, Reynolds, & Lowe, 2001). However, because attention and EF are such multifaceted but similar constructs, it is difficult to link specific individual neuropsychological behaviors of interest through one-to-one correspondence to specific neurological components or brain structures (Mirsky, Fantie, & Tatman, 1995a). The various models of attention and EF, however, consistently implicate a complicated functional system involving interactions among cortical structures (frontal, prefrontal, parietal, and temporal), subcortical structures

(limbic system, basal ganglia, reticular activating system), and projections to/from the thalamus and frontal lobes (Cohen & O'Donnell, 1993; Luria, 1966; Riccio et al., 2001).

Mirsky's Model of Attention

Allan F. Mirsky is one researcher that has contributed to the knowledge base on attention problems. Mirsky and his colleagues (Mirsky, 1987, 1989, 1996; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Mirsky et al., 1995a; Mirsky, Ingraham, & Kugelmass, 1995b; Mirsky, Pascualvaca, Duncan, & French, 1999) have posited a neuropsychological model to describe the elements of impaired attention. The model hypothesizes that each element (including the ability to sustain, encode, focus, regulate, and shift attention) is supported by distinct cerebral regions, and can be assessed with specific neuropsychological tests. This approach has demonstrated that attention is not a unitary brain process, but comprises a group of highly articulated functions.

Contributions to the Model

Mirsky's model of attention was originally developed from a developmental-evolutionary perspective that examined the brain as a "triune" structure (MacLean, 1990). This structural model analyzed the core processes of attention as a predominantly brain stem system that existed for millions of years and continues to exist in the brains of modern reptiles (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). The reptilian portion of the brain consists of the gray matter in the cerebrum, along with portions of the basal ganglia including the caudate, putamen, globus pallidus, and connections to the thalamus and pontine regions of the brain stem (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This region is overlaid by the paleomammalian brain, which includes the limbic system of the brain (e.g., the

amygdala, hippocampus, cingulate gyrus). Finally, the neomammalian brain is comprised of neocortical structures and thalamic connections. Mirsky's stance for supporting this developmental-evolutionary perspective is that MacLean (1990) has shown that the reptilian brain can support many behaviors that could be characterized as sustained or attentive, and newer cortical structures from an evolutionary standpoint provided the means for additional capacity for attentive behavior. The capacity for visual attention in infants (Lansink & Richards, 1997; Lawson & Ruff, 2004) has been cited as reasoning that sustained attention can be supported prior to complete myelination of the neocortex, providing further evidence for this connection made by Mirsky.

Another theoretical contribution to Mirsky's model of attention came from research on the early development of the original continuous performance test (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) and research on the study of epilepsy (Penfield & Jasper, 1954). The CPT was a landmark assessment tool for the neuropsychological measurement of attention when it was pioneered in the mid-1950s, as it could differentiate between "brain-injured" and "non-brain-injured" groups among various samples including adults with normal intelligence, children with normal intelligence, and persons diagnosed with mental retardation (Rosvold et al., 1956). Further inquiry into the link between brain injury and impairments on the CPT suggested that damage to midline subcortical brain regions was most related to impairment in sustained attention on the CPT (Mirsky & Van Buren, 1965).

Individuals who demonstrated the most accurate portrayal of this attention profile suffered from absence epilepsy, which was earlier referred to as centrencephalic epilepsy (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). The term

“absence” was used for these patients because of their brief moments of unresponsiveness during which interruptions of attention occurred simultaneously as abnormal EEG patterns (Mirsky & Van Buren, 1965). Earlier research by Penfield and Jasper (1954) indicated that the centrencephalic system was located at the level of the brain stem reticular formation and midline thalamus, and it served as a major organizational center devoted to consciousness, arousal, and attention (Lindsley, 1960; Penfield & Jasper, 1954). The centrencephalic disturbances associated with absence epilepsy were later designated as corticoreticular in nature because of the linkage between subcortical reticular disturbances in the brain stem region and their connections to cortical structures (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This line of reasoning was in keeping with the reptilian portion of MacLean’s (1990) “triune” brain, suggesting that individuals with disturbances in vigilance or sustained attention exhibited some pathological involvement of the corticoreticular system (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999).

In this sense, the predominant theme within current research suggesting that attention represents a complex set of highly coordinated processes in the brain concurred with the developmental-evolutionary and centrencephalic/corticoreticular perspectives of the brain’s structural involvement (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This coordinated system of attention proposed connections among neocortical, limbic, and cerebral regions through centrencephalic/corticoreticular pathways to form the basic foundation of Mirsky’s model of attention (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This view also followed with contemporary information-processing theories of attention that linked many different

mental operations to attention, including selectivity, focusing, sustained vigilance, switching attention, rehearsal, coding, and retrieval (Mirsky, 1996; Mirsky et al., 1999; Posner & Petersen, 1990; Shiffrin, 1988). Mirsky and colleagues proposed a "restricted taxonomy of attentive functions" that was based on results from neuropsychological test data and subsequent factor analyses on over 600 subjects, most of whom had various disturbances of attention functions (Mirsky, 1996; Mirsky et al., 1999).

Attention domains

The restricted taxonomy of attention included five domains comprising focusing/executing, sustaining, stabilizing, shifting, and encoding behaviors, each of which tap specific attention functions, could be measured by various neuropsychological tests, and were linked to specific brain regions (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This organization created a system of shared responsibility in which functional and structural specialization was not absolute, allowing some degree of substitution in the event of an injury (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). The five domains of Mirsky's model are reviewed below.

Focus/Execute. The attention domain of Focus/Execute deals with the ability to concentrate attentional resources on a task, while screening out distracting stimuli usually under timed conditions (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). In their effort to isolate this domain, Mirsky and colleagues had difficulty separating this aspect of attention from executing, which refers to the task demand of rapid response (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). Tests used to measure this attention function include the Digit Symbol Substitution subtest from the Wechsler Adult Intelligence Scale – Revised (WAIS-R), the Stroop Test,

and the Trail Making test (Parts A & B) from the Halstead-Reitan Battery. The function of focusing on environmental events involves the superior temporal cortex, inferior parietal cortex, and the corpus striatum regions of the brain, while the execution of responses involves the inferior parietal and corpus striatum regions (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999).

Sustain. The attention domain of Sustain deals with an individual's ability to stay on-task for an extended period of time in a vigilant manner (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). Variables that measure the number of correct targets an individual selects from various CPTs can tap into sustaining attention, including both visual and auditory stimuli. Mirsky and colleagues (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999) have demonstrated that rostral midbrain structures, including the mesopontine reticular formation and midline/reticular thalamic nuclei, are associated with the ability to sustain attention.

Stability. Related to one's capacity to sustain attention, the attention domain of Stability refers to the ability to maintain consistency within a predictable response pattern over time (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). This can include measuring the variability of reaction time to target stimuli on CPTs, along with the variability of correct or incorrect response patterns among consecutive blocks of trials within an administration of the CPT (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). The stability function is said to be dependent upon several regions, including midline-thalamic and brain stem structures (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999).

Shift. The attention domain of Shift deals with the ability to move from one salient aspect of a stimulus to another in a flexible, efficient manner (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). The hallmark measure used to assess this attention domain is the Wisconsin Card Sorting Test (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999), although other measures that tap into problem-solving over varying trials, such as the Tower of London and Tower of Hanoi tasks, have also been used as measures of set-shifting in other studies (Gipson et al., 2006; Hooper, Swartz, Wakely, de Kruif, & Montgomery, 2002). The brain regions purported to be involved with this function include the dorso-lateral prefrontal cortex, specifically the anterior cingulate gyrus (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999).

Encode. Mirsky and colleagues have consistently identified the attention domain of Encode, which involves a mnemonic capacity related to working memory that allows individuals to hold information briefly in their mind while performing a cognitive operation on this information (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). Various digit span subtests have been consistently used to measure this aspect of attention within Mirsky's model. The encoding function is maintained within brain regions associated with the limbic system, including the hippocampus and the amygdala (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999).

Considerations

Despite the large amount of research backing the claims in this model of attention, there are certain factors to consider when one examines its place within the entirety of previous research of attention. Within the larger scheme of things, the contribution of

Mirsky's model of attention to the field does provide clarity to the available literature from a neuropsychological framework. There exists a dearth of studies that have linked functional domains to various structural regions within a model of attention using test data to support this claim; therefore, Mirsky's model is unique and convincing in this respect. However, the study of attention, memory, and EF has become increasingly complex and muddied throughout the years because of the varying conceptual and theoretical bases used by different researchers (Lyon, 1996; Morris, 1996). The fuzzy boundaries have created varying constructs and measurement models among researchers, and a measure used in one study for testing attention may also be used occasionally in another study to test EF (Morris, 1996). This theoretical overlap has been addressed previously (Gibson & Rader, 1979; Morris, 1996), and researchers have struggled with separating these three functions to adequately address construct validity (Fletcher et al., 1996). For instance, domains utilized in Mirsky's model of attention have some degree of overlap with models of executive functions (Daigneault, Braun, & Whitaker, 1992; Denckla, 1996). Therefore, it is important to consider this overlap among various models when studying attention, in addition to the specific contributions that each model provides on its own accord.

Mirsky's model of attention is utilized in the current study as a means to measure attention in children with CKD for a number of reasons. The historical context of this model as it relates to previous research on individuals with epilepsy, in addition to the contribution from the development of the original CPT, both provide empirical bases to support its connection to developmental-evolutionary and multi-component information processing perspectives. Furthermore, Mirsky's use of a factor structure to generate this

model appears to lend additional strength to its utility with a pediatric CKD population that most executive function models have not utilized. In short, Mirsky's model incorporates strengths from the various models of attention proposed to date, while simultaneously providing a broad framework to conceptualize the multidimensional construct of attention.

Previous Applications of Mirsky's Model of Attention

Several studies have utilized Mirsky's (1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999) neuropsychological model to characterize the specific domains of attention observed in various populations. Researchers have recognized Mirsky's contribution to the attention literature by speaking of their attention battery as aligning with the multiple domains of this model, but relatively few studies actually assess every domain with the suggested tests or validated analogs. The populations examined in these comprehensive studies are quite varied, with insight provided on specific attention domains within Mirsky's model for individuals with CKD, post-traumatic stress disorder (PTSD), autism, congenital hypothyroidism, prenatal teratogen exposure, and postnatal lead exposure. Examining these studies can provide valuable insight as to how specific attention domains in children with CKD may be portrayed through Mirsky's model.

Chronic Kidney Disease. Yount and colleagues (1998) utilized the original model posited by Mirsky (1987) as a framework to examine specific attention domains in adults with CKD. These researchers examined data from 554 adults with ESRD in an effort to identify potential psychosocial and biomedical predictor variables (Yount et al., 1998). Results suggested three underlying factors including sustained attention, focused attention, and memory recall (Yount et al., 1998). Sustained attention was comprised of

CPT data, including Total Correct, Mean Response Time, and Variance scores. Focused attention was comprised of data from the Stroop Color-Word test, Trail Making Test Part B, and Digit Span Forward. Memory recall was comprised of data from total and delayed free recall scores. Sustained attention and memory recall were found to only be associated with gender. Focused attention was found to be most strongly associated with psychosocial and biomedical variables, with younger age, less severe CKD, higher education levels, and higher vocabulary scores being positively correlated, and use of hemodialysis being negatively correlated, with better performance in this domain. These findings were consistent with previous findings in adult CKD samples (Pliskin, Yurk, Ho, & Umans, 1996; Wolcott et al., 1988). The results from this study also provide empirical evidence indicating inconsistencies among the various domains of attention in a sample of adults with CKD, which suggests possible generalization of this profile to children with CKD.

Post-traumatic Stress Disorder. The available literature has also produced mixed findings regarding the potential for neuropsychological dysfunction to result from extreme psychological stress and emotional dysregulation, although more consistent negative outcomes in the areas of attention, memory, learning, and organizational processes have been reported for prisoner of war survivors. However, the co-occurrence of biological and psychological insults for these individuals makes it difficult to fully characterize neuropsychological dysfunction in this population as only due to psychological stress (Vasterling et al., 1998). To this end, adults with PTSD who served in the first Persian Gulf War were assessed on measures of attention and memory on a battery of tests designed to load onto analogous constructs from Mirsky's model of

attention (Vasterling et al., 1998). Less proficient attention performance was noted based on scores on the WAIS-R Arithmetic and Commissions portion of the CPT, suggesting difficulties with encoding abilities and sustained attention when compared to veterans without PTSD (Vasterling et al., 1998). This pattern of results suggested a tendency towards response disinhibition for individuals with PTSD that have consistent re-experiencing episodes.

Autism. For children with autism, attention is a difficult construct to measure due to the confounding influence of their inability to function socially. Using Mirsky's model of attention, a research team attempted to quantify the degree and type of attention dysfunction in a sample of 23 children with autism. Contrary to findings in the adult PTSD literature, school-age children with autism exhibited intact focus and sustained attention capacities based on performance similar to the control groups on digit cancellation and CPT tasks (Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998). However, there was considerable evidence suggesting the possibility of difficulties with disengaging on shifting tasks (e.g., the Wisconsin Card Sorting Task – WCST). However, using two novel computerized measures of shifting attention, the researchers found that children with autism performed similarly to controls. These findings lend evidence to the available literature indicating that individuals with autism have adequate attention capacities that are consistent with repetitive behaviors despite a tendency to not disengage from a particular stimulus (Pascualvaca et al., 1998). Similar findings have been replicated in subsequent studies, with factor analysis indicating diminished performance on the focus/execute and shifting components, but not for sustain or encode

components, of Mirsky's model of attention for individuals with high functioning autism (Goldstein, Johnson, & Minshew, 2001).

Congenital Hypothyroidism. Individuals with congenital hypothyroidism (CH) also evidence difficulties with attention secondary to fluctuating thyroid hormone levels (Rovet & Hepworth, 2001). Research on deficient thyroid hormone levels in animal models has suggested that problems with neurodevelopment may result, with a particular impact on cortical structures that later become important for attention such as the hippocampus, parietal cortex, and caudate, each of which is highly thyroid hormone dependent (Bernal & Nunez, 1995; Rovet & Hepworth, 2001). Using a retrospective design to examine previous attention data from adolescents with CH, Rovet and Hepworth (2001) attempted to characterize specific attention deficits in this population using Mirsky's model of attention. Attention deficits were evident for adolescents with CH compared to a control group, with particular deficiencies noted on focus and inhibit indices based on poorer performance than controls on CPT Commissions, Trail Making Test Part A, WCST Accuracy and Perseverative Errors, and WISC-R Coding (Rovet & Hepworth, 2001). Furthermore, specific attention deficits were correlated with certain disease parameters, such as more severe levels of hypothyroidism and longer duration of low thyroid hormone levels being associated with lower scores on the encode and focus indices, which provide an interesting finding that may potentially be compared to children with CKD (Rovet & Hepworth, 2001). However, it is important to consider the implications of treatment differences between CH and CKD patients as it relates to attention in these populations, because thyroid hormone therapies are very effective

treatments for alleviating thyroid dysfunction whereas treatments for CKD that restore kidney function do not exist.

Fetal Alcohol Exposure. Children whom experience fetal alcohol exposure (FAE) also run the risk of global and specific neuropsychological impairments. Several studies on children with FAE have used case-control comparisons and principal components analysis (PCA) to replicate Mirsky's findings on the multicomponent model of attention in this population (Burden, Jacobson, Sokol, & Jacobson, 2005; Coles, Platzman, Lynch, & Freides, 2002). Burden and colleagues (2005) examined the relationship between FAE in elementary school children and empirically derived attentional constructs from Mirsky's model of attention using PCA on the ten measures Mirsky utilized, in addition to a second PCA on the ten measures used by Mirsky and four additional measures used to examine working memory and executive function domains. Their results were similar for both the original and extended PCAs, with factors reflecting elements of encode, shift, focused/sustained attention, along with a distinct element dealing with impulsivity (Burden et al., 2005). Among the domains of attention identified in these PCAs, FAE was most strongly associated with poor working memory, comprised of digit span, arithmetic, and digit cancellation tasks (Burden et al., 2005). Adolescents with FAE have also been shown to be less efficient in processing stimuli requiring visual attention than their healthy peers, despite similar performance on auditory attention tasks (Coles et al., 2002). Similar findings have also been reported for adolescents who were prenatally exposed to cigarettes and marijuana, with PCA results yielding a five-factor model very consistent with Mirsky's (Fried & Watkinson, 2001). Prenatal cigarette exposure was most associated with deficits in encode and impulsivity components of attention, and

prenatal marijuana exposure was most associated with deficits in attention stability (Fried & Watkinson, 2001).

Postnatal Lead Exposure. Research on children with low levels of postnatal lead exposure has also indicated the potential for neurocognitive deficits, particularly within the domains of attention and executive functions (Chiodo et al., 2004). Chiodo and colleagues (2004) assessed the neurodevelopmental effects of low levels of postnatal lead exposure in African American urban youths. Specific aspects of attention were measured in this sample using Mirsky's model of attention, and results suggested that lead exposure at least partially accounts for deficits in sustained attention based on lower total correct scores on auditory and visual CPT (Chiodo et al., 2004). Differences were also noted within the executive functions domain on the WCST task and a verbal fluency task (Chiodo et al., 2004). Regression analyses confirmed associations between neuropsychological dysfunction and low doses of lead exposure, suggesting that a lower bound threshold for postnatal lead exposure leading to these deficits was not evident (Chiodo et al., 2004). This latter finding was interesting given the similarities between this population and children with CKD who have varying levels of native kidney function and fluctuating levels of uremic toxins in the blood.

Overall, it appears that attention as characterized into multiple domains in Mirsky's model has been deemed susceptible to the presence of several psychiatric and medical conditions in children, adolescents, and adults. However, there appears to be considerable variability in the type of attention deficits noted in Mirsky's model among these conditions. Adults with PTSD and children with prenatal exposure to teratogens appear to have deficits in the encode and sustain domains, while children with autism

tend to struggle more on tasks associated with the shifting domain of attention, as one might expect given the behavioral phenotype of autism. Conversely, adolescents with CH tend to have difficulty with tasks on the focus and inhibit domains, and children with postnatal lead exposure have difficulty on sustained attention tasks. Yount and colleagues (1998) also showed that various psychosocial and biomedical variables were predictive of focused attention in adults with CKD, which has implications for the current study. Based on this literature, there appears to be sufficient basis to compare how children with CKD manifest deficits within specific attention domains within Mirsky's model of attention.

Attention Functioning in Pediatric and Adult CKD

The findings in the pediatric CKD literature are mixed with respect to the domains of attention (Fennell et al., 1990a, 1990b; Gipson et al., 2006; Mendley & Zelko, 1999; Qvist et al., 2002). In one of the first studies to examine attention in this pediatric population, Rasbury and colleagues (1983) administered the Continuous Performance Task (Rosvold et al., 1956; Gale & Lynn, 1972) to children and adolescents with CKD. No significant differences were found on this task between controls and ESRD patients at baseline or 1-month after receiving a transplant. Fennell and colleagues (1990a, 1990b) have also reported no differences in measures of sustained attention within a heterogeneous sample of children with all treatment modalities of CKD versus matched controls. The degree of attention impairment was related to an earlier age of onset and duration of the CKD. More recently, Mendley and Zelko (1999) reported improvements in sustained attention and mental processing speed one year after transplant in their sample of 9 children with CKD. Additionally, Qvist and colleagues (2002) reported no

group deficits of attention in their renal transplant sample when compared with the normative population from the NEPSY, although 24% of their sample evidenced generalized attention deficits (defined as scaled score < 7 or SS < 85).

Using a multidimensional model of executive functioning (i.e., Initiating, Sustaining, Set-Shifting, Inhibiting), Gipson and colleagues (2006) recently reported on the presence of significant problems in selected executive functions in their sample of children with CKD when compared to a typically-developing comparison group. The CKD group performed poorer than the control group in the Initiation and Sustaining domains, after controlling for chronological age and IQ. The groups did not differ on Set-Shifting or Inhibition. These findings suggested the possibility that the progression of renal disease may disrupt selected aspects of attention and executive functions beyond the generalized effects of lower IQ. With this same sample of CKD patients, Slickers and colleagues (2007) also recently identified associations between clinical variables and specific neurocognitive deficits. In this study, attention and disease severity were not correlated significantly (Slickers et al., 2007); however, prospective memory was significantly correlated with higher levels of disease severity ($p < .01$) and longer duration of disease ($p < .04$) in this sample (Slickers et al., 2007).

In adults with CKD, studies have generally examined the integrity of attention in patients with CKD as it relates to kidney failure and, more specifically, the effects of dialysis treatment. Heilman and colleagues (1975) reported significant differences between uremic (ESRD) patients and controls on immediate memory, which was postulated to manifest through poor arousal due to complications of uremia and below average rehearsal skills. These difficulties with higher-order cortical functions on novel

problem-solving tasks have been replicated elsewhere (Ginn, 1975; Souheaver, Ryan, & DeWolfe, 1982), and suggested a specific pattern of deficits in attention and executive domains for adults with CKD (Hart, Pederson, Czerwinski, & Adams, 1983; McDaniel, 1971). This coincided with a previously widely held belief that uremia and ESRD reduced global attention functioning (Marshall, 1979; Nissenson, Levin, Klawans, & Nausieda, 1977; Stewart & Stewart, 1979). However, these findings have been inconsistent with other results (Heilman et al., 1975; Souheaver et al., 1982) suggesting intact auditory attention for tasks requiring passive reception of auditory stimuli and minimal organization of verbal material (e.g., Digit Span tasks).

Additionally, previous studies that measured performance on CPTs with adult CKD patients have been inconclusive regarding differential performance patterns in this population (Alexander, Hightower, Anderson, & Snow, 1980; Rasbury, Fennell, Eastman, Garin, & Richards, 1979; Umans & Pliskin, 1998). Slowed reaction time has been implicated in at least one previous study with adults with uremia (Alexander et al., 1980); nevertheless, other CPT variables (e.g., errors of omission and commission, total correct, variability) have not shown differential performance patterns for patients with CKD. In this sense, the available studies on attention processes in adults with CKD are inconsistent and suffer methodological limitations (e.g., small sample sizes, wide age ranges, heterogeneous severity of kidney failure within samples, adequacy of dialysis delivery not assessed) that make generalization of these findings in the contemporary ESRD population difficult.

Similar to findings in the pediatric CKD literature, neuropsychological performance, and specifically attention functioning, has also been reported to improve

after transplantation and hemodialysis in adults with ESRD. Teschan and colleagues (1976) found significant improvements in choice reaction time and memory scores following transplant in adults with ESRD. In a later study that included a heterogeneous group of adult CKD patients and a control group, Teschan and colleagues (1979) found that transplant patients performed at a comparable level to the control group on attention and working memory tasks, although results comparing the dialysis and transplant groups were not presented. More recently, several studies have reported improved performance after renal transplantation in adults on tests of attention, executive function, and working memory (e.g., Trail Making Test, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test) and on EEG patterns (Griva et al., 2004; Kramer et al., 1996).

The temporal effects of different types of dialysis (e.g., hemodialysis versus peritoneal dialysis) on attention in adults with ESRD have also been examined recently (Griva et al., 2003). This is an important consideration to make, as peritoneal dialysis is a continuous treatment that patients undertake on a daily ongoing basis whereas hemodialysis requires approximately three dialysis sessions per week when purified water filtration of the patient's blood is conducted. The research on the potential temporal effects on attention differences for hemodialysis versus peritoneal patients has suggested significantly greater improvements on tasks of attention, concentration, and memory in hemodialysis patients 24-hours post-dialysis than for peritoneal dialysis patients who typically received daily therapy (Griva et al., 2003).

Overall, it appears that scores of attention and executive functions are lower than normal to a certain degree in both pediatric and adult CKD patients. The available literature is inadequate to fully characterize this effect among renal replacement

modalities or severity of renal disease with regards to specific aspects of attention, and findings are somewhat inconsistent. Further research is warranted in this particular area of neurocognitive functioning to examine attention functions in children with CKD.

Attention Functioning in Other Pediatric Medical Conditions

Recent research on medical illnesses has increasingly focused on the link with, and the potential functional consequences of, attention and executive impairments. However, the medical literature has not yet developed to the point of using meta-analysis techniques to systematically review the degree of attention and executive dysfunction across various medical illnesses (Schillerstrom, Horton, & Royall, 2005). Studies on children and adults with modest sample sizes have found modest to strong associations between impairments in attention and executive functions and several medical illnesses (Schillerstrom et al., 2005), including diabetes (McAulay, Deary, Sommerfield, & Frier, 2005; Rovet & Alvarez, 1997), spina bifida (Dennis et al., 2006), sickle cell disease (Kral et al., 2001; Noll et al., 2001), pediatric HIV/AIDS (Armstrong et al., 2003; Bisiacchi et al., 2000; Brouwers et al., 1994), and cancer (Vannatta & Gerhardt, 2003). Examining the differential effects of attention and executive dysfunction in these medical populations may provide additional insight into the impact of attention deficits for children with CKD.

Diabetes

Children with diabetes mellitus face a variety of neurocognitive complications associated with suboptimal control of glucose levels. With regards to the integrity of attention in this population, acute episodes of hypoglycemia have been consistently linked to generalized attention deficits in adults with Type 1 diabetes (McAulay et al.,

2005) while children and adolescents with Type 1 diabetes demonstrate differential performance among specific domains of attention (Rovet & Alvarez, 1997). Specifically, children and adolescents with Type 1 diabetes with a history of hypoglycemic seizures and higher blood glucose levels have demonstrated more difficulties than healthy controls with the selecting, focusing, and inhibiting components of attention, along with intact sustaining, suppressing, and shifting attentional components (Rovet & Alvarez, 1997). These attention deficits have been found not to resolve up to six years after initial diagnosis, particularly for children with onset of Type 1 diabetes prior to 4 years of age (Northam et al., 2001). Single-subject design studies have also shown that children with Type 1 diabetes engaged in off-task classroom behavior between 23%-39% of time observed prior to the introduction of an insulin pump (Daley, Wodrich, & Hasan, 2006). In summary, cognitive impairments, such as deficits in attention and mental processing, for children with Type 1 diabetes tend to be linked to physiological factors associated with this disease, including earlier age of onset and moderate to severe episodes of hypoglycemia (Ferguson et al., 2005; Hannonen, Tupola, Ahonen, & Riikonen, 2003; Kaufman, Epport, Engilman, & Halvorson, 1999; Ryan, Vega, & Drash, 1985; Ryan et al., 1990).

Spina Bifida

Children and adolescents with spina bifida face a variety of neurocognitive problems associated with incomplete neural tube formation during early prenatal development (Dennis et al., 2006). Deficits in attention orienting have been reported in infants with spina bifida on tasks of facial saliency (Landry, Lomax-Bream, & Barnes, 2003). School-age children with spina bifida, when compared with their healthy peers,

have been shown to orient more slowly and take longer to disengage from stimuli that have captured their attention (Dennis et al., 2005a). Current estimates on the prevalence of children with spina bifida meeting criteria for ADHD has suggested that rates exceed that of the general population, ranging between 30-40%, with ADHD-Inattentive type being more predominant (Burmeister et al., 2005; Davidovitch et al., 1999). Inhibition of return (i.e., a visual search technique in which additional time is required to locate a target stimulus in a previously attended location, as a means to increase the likelihood of locating new targets in new locations; Posner & Cohen, 1984) has also proven to be problematic in this pediatric population, as brain dysmorphologies of the midbrain (e.g., superior colliculus) have been linked to this covert shifting of attention (Dennis et al., 2005b). Deficits in arithmetic processing skills have also been documented in children with spina bifida, with connections made to attention through accompanying visual-spatial and processing speed deficits (Ayr, Yeates, & Enrile, 2005; Barnes et al., 2006). Neurocognitive deficits, particularly in the areas of executive dysfunction and distractibility, also tend to be more prevalent for children with spina bifida and accompanying hydrocephalus (Horn, Lorch, Lorch, & Culatta, 1985; Iddon, Morgan, Loveday, Sahakian, & Pickard, 2004).

Sickle Cell Disease

Research on the cognitive functioning of children with sickle cell disease (SCD) has indicated domain-specific deficits in attention for this pediatric population (Brown et al., 1993; Kral et al., 2001). This is evident for children with SCD with (Brown et al., 2000; DeBaun et al., 1998) and without (Noll et al., 2001) a history of previous overt or silent strokes, with the frontal lobe proposed as the primary site of injuries. Recent

research has also suggested that the cortical location of ischemic lesions and infarcts have direct implications on attention in children with SCD (Schatz et al., 1999). Attention deficits and executive dysfunction in pediatric SCD patients have been linked to anterior cerebral infarcts (Schatz et al., 1999). Global intellectual deficits and academic problems appear to be more common for children with SCD and overt strokes (Armstrong et al., 1996; Swift et al., 1989), and global neurocognitive delays can occur as early as within the first 3 years of life (Thompson, Gustafson, Bonner, & Ware, 2002). The literature seems to indicate that specific domains of neurocognitive functioning should be examined for children with SCD, particularly for those with overt and/or silent strokes (Kral et al., 2001; Lemanek et al., 2003; Schatz et al., 1999).

Pediatric HIV/AIDS

Deficits in attention have also been reported in school-age children with HIV infection. However, the research is limited with respect to older children and adolescents because of the small number of trials being conducted and because cohorts of children with HIV/AIDS are only recently beginning to survive in larger numbers to participate in these studies, with the help of antiretroviral therapies (Armstrong et al., 2003). Given the progressive course of pediatric HIV/AIDS and the long-term implications of antiretroviral therapies, adolescents and young adults have been shown to exhibit neurocognitive deficits and symptoms consistent with AIDS-related dementia in the adult HIV literature (Armstrong et al., 2003; Melton, Kirkwood, & Ghaemi, 1997), with memory and frontal lobe functions such as impaired judgment and reasoning being the most impacted (Simpson & Berger, 1996). Findings with respect to attention in school-age children are somewhat inconsistent (Armstrong et al., 2003). Although some

children may appear asymptomatic at a given age in school and global cognitive deficits tend to be rare, recent estimates suggest that executive functioning and attention problems are specifically common in both preschool and school-age children with HIV/AIDS (Bisiacchi et al., 2000; Brouwers et al., 1994). In fact, other research has suggested that possibly half of children with HIV/AIDS experience significant enough school difficulties from specific functional deficits to warrant special education services (Mialky, Vagnoni, & Rutstein, 2001). Researchers have speculated on the impact of HIV on the development of specific attention mechanisms in the developing brain (Armstrong et al., 2003), as neurological compromise due to cerebral atrophy, ventricular enlargements, cerebral calcifications, reduction of white matter, and demyelination contribute to CNS and static encephalopathy in pediatric HIV/AIDS (Mintz, 1999). In this sense, the literature suggests that subtle neurocognitive impairments may be an additional consideration for pediatric HIV/AIDS patients, even if CNS problems and impaired neurodevelopment early in life do not exist for an individual (Armstrong et al., 2003; Pearson et al., 2000).

Pediatric Cancer

The available literature suggests that neurocognitive deficits are evident for pediatric cancer patients with brain tumors, those that receive cranial radiation, and those that receive intrathecal chemotherapy to decrease CNS involvement of acute lymphoblastic leukemia (ALL; Butler & Copeland, 1993; Powers, Vanatta, Cool, & Stehbens, 1995; Vannata & Gerhardt, 2003). Among neuropsychological domains tested in recent studies, deficits for pediatric cancer patients with CNS involvement have been apparent in the broad areas of intelligence, memory, attention, and academic functioning

(Lockwood, Bell, & Colegrove, 1999; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000; Schatz, Kramer, Ablin, & Matthay, 2000). With regards to attention, Lockwood and colleagues (1999) have provided evidence of global attention deficits for children whom have undergone cranial radiation, with differences noted for both fundamental attention processes (e.g., focusing, tracking, shifting), complex executive skills (e.g., mental switching, hypothesis formation, problems solving), and sustained attention. In fact, studies have shown that irradiated childhood ALL survivors demonstrate many ADHD-like symptoms, including distractibility and difficulty with sustained attention (Brouwers & Poplack, 1990). This propensity for attention problems has also been reflected in elevated rates of special education placements in this population (Haupt et al., 1994). Visual attention has been shown to be a specific deficit for children with ALL, with difficulties on attention shifting tasks being directly related to cranial radiation (Schatz, Kramer, Ablin, & Matthay, 2004). Sustained attention has also been found to improve with methylphenidate treatments in double-blind placebo studies, with post-treatment improvements noted on CPT measures of errors of omission (Thompson et al., 2001). CNS treatment and subsequent neurocognitive effects have tended to be worse for children who are younger at initial diagnosis (Lockwood et al., 1999; Vannatta & Gerhardt, 2003).

Considerable evidence also exists indicating that neurocognitive deficits in pediatric cancer patients expand to include broader difficulties with adjustment and social functioning, including problems with social withdrawal, diminished friendships, and less involvement in social activities (Carpentieri, Mulhern, Douglas, Hanna, & Fairclough, 1993; Radcliffe, Bennett, Kazak, Foley, & Phillips, 1996; Vannatta, Gartstein, Short, &

Noll, 1998). Findings in these studies reflecting poorer psychosocial function for children with CNS malignancies are mirrored by findings in the pediatric traumatic brain injury (TBI) literature indicating poorer psychosocial outcomes for children who have sustained a TBI versus only orthopedic injuries (Andrews, Rose, & Johnson, 1998; Bloom et al., 2001). For children with ALL, emerging evidence suggests that younger patients who undergo higher intensities of neurotoxic treatment are at considerable risk for both neurocognitive and social dysfunction (Chen et al., 1998; Hill et al., 1998; Vannatta, Zeller, Noll, & Koontz, 1998).

Because of the dearth of studies available on this topic, it is unclear whether children with brain tumors consistently experience emotional and behavioral dysfunction that could indirectly impact attention capacities (Vannatta & Gerhardt, 2003). The research has been inconsistent with this particular population, taking into account conflicting findings suggesting significant problems with emotional regulation upon parent report in addition to low scores on measures of depression upon self-report (Radcliffe et al., 1996). In this sense, similar to findings regarding social functioning in pediatric patients with CKD, it remains to be seen whether findings suggesting emotional distress among brain tumor survivors reflect methodological issues related to comparing clinical samples to normative samples, parent report of distress that children do not actually experience, or an adaptive style in which brain tumor survivors repress emotional distress and do not inherently acknowledge its presence (Vannatta & Gerhardt, 2003).

In summary, based on the available literature, it appears that attention and executive functions are quite vulnerable in the presence of a variety of chronic medical

conditions in childhood. These neurocognitive deficits have been linked to earlier age of disease onset, more severe forms of disease, accompanying comorbid conditions, cortical defects, treatments affecting CNS functioning, higher rates of special education placement, and decreased levels of adjustment or social functioning. Based on this literature, there is a need to examine this question in children with CKD.

Associations Among Clinical Variables and Neurocognition

The relationship between medical variables associated with certain medical conditions have received increased acknowledgement recently in the literature as to the detrimental effects on neurocognition. Three medical outcomes often associated with CKD patients are disease severity (eGFR), anemia, and hypertension. A brief review of the literature on these topics is covered below, in an attempt to conceptualize how attention may differ among children with CKD with these considerations.

Slickers and colleagues (2007) have provided a contemporary examination of clinical predictors for neurocognitive dysfunction in children with CKD. In their study, attention was operationally defined as the total number correct variable from the Gordon Diagnostic System, a visual CPT. Results indicated that lower IQ and memory scores were correlated with increased disease severity. Lower memory scores were also correlated with longer duration of disease, while lower IQ scores were correlated with greater percentage of life with CKD (Slickers et al., 2007). Although attention was not linearly associated with disease severity in this sample, Slickers and colleagues (2007) reported that dichotomous comparisons between patients with mild/moderate CKD to those with severe CKD/ESRD yielded significant differences on IQ, memory, and

attention. Anemia and hypertension did not correlate significantly with IQ, memory, or attention in this sample (Slickers et al., 2007).

The issue of disease severity has also been tackled in several other studies examining neurocognitive dysfunction in CKD, but most studies to date have focused primarily on children with ESRD. Although it seems logical that CKD severity would be proportional to the degree of cognitive impairment, the data are not yet available to completely support this finding in the CKD population. Results from the study by Slickers and colleagues (2007) argue against a threshold effect of CKD severity on neuropsychological outcomes; in this sense, children at all stages of CKD severity are potentially at risk for neuropsychological deficits. These findings have also been replicated with respect to children with CKD on dialysis compared with children who have previously undergone a kidney transplant (Brouhard et al., 2000; Lawry et al., 1994). This association between disease severity and poorer neuropsychological outcomes is also supported by previous research in other medical populations, including Type 1 diabetes (Northam et al., 2001; Rovet & Alvarez, 1997), spina bifida (Horn et al., 1985; Iddon et al., 2004), sickle cell disease (Kral et al., 2001; Schatz et al., 1999), pediatric HIV/AIDS (Armstrong et al., 2003), and pediatric cancer (Lockwood et al., 1999; Vannatta & Gerhardt, 2003).

The link between poor health outcomes and low hemoglobin/hematocrit levels is also clear in the literature, due to findings related to CKD, congestive heart failure, chronic inflammatory bowel disease, and rheumatoid arthritis (Eknoyan, 2001; Silverberg, Iaina, Wexler, & Blum, 2001). The association between decreased cognitive function and anemia has been most widely examined in the CKD patient population

(Marsh et al., 1991; Nissenson, 1992; Stivelman, 2000). Stivelman (2000) has recently reviewed this topic to highlight several studies investigating the use of erythropoietin (EPO) in adult CKD patients with anemia. Among them is a study by Marsh and colleagues (1991) that demonstrates an association between raising hematocrit levels and improvements on electrophysiological and neuropsychological measures. Significant improvements were noted between pre- and post-EPO treatment on P300 event-related potential (ERP) amplitudes and on the executive function tasks of Symbol-Digit Modalities Test and Trail Making Test, Part B (Marsh et al., 1991). Similar improvements on P300 ERP latencies, EEG findings, and neuropsychological tests have been reported elsewhere (Brown et al., 1991; Grimm et al., 1990; Nissenson, 1992; Sagales et al., 1993). Pickett and colleagues (1999) have further advanced this position with their work on the relationship between neurocognitive functioning and altogether eliminating anemia in their patients. In this study, patients on hemodialysis (n = 20) had their hematocrit levels normalized with EPO and experienced accompanying decreases in EEG slowing at higher hematocrit levels (Pickett et al., 1999). Taken together, these findings seem to suggest a direct positive relationship between hematocrit/hemoglobin levels and higher-order cognitive functions such as attention span in CKD patients (Stivelman, 2000), and provides a basis for determining whether differential performance among neuropsychological measures of attention exist in a pediatric sample of CKD patients.

The association between blood pressure and cognitive decline in adults, particularly for the elderly, has been firmly established in the literature (Starr, 1999; Suhr, Stewart, & France, 2004). However, this association has not been examined as

extensively for pediatric patients with elevated blood pressure, particularly given the recent trend of increasing prevalence of obesity among today's youths (Muntner, He, Cutler, Wildman, & Whelton, 2004). Hypertension in the general pediatric population has been correlated with decreased performance in tasks requiring memory, attention and concentration (Lande et al., 2003). In this population-based study by Lande and colleagues (2003), school-age children from a U.S. survey were diagnosed with hypertension on the basis of an averaged right arm systolic or diastolic blood pressure above the 90th percentile for age, height and gender. Hypertension was independently associated with significantly lower neurocognitive scores representative of short term memory, attention, and concentration problems, as measured by various digit span test scores (Lande et al., 2003). This work by Lande and colleagues (2003) represents the only population-based study on hypertension in children and adolescents.

Retrospective studies of pediatric patients with CKD have similarly demonstrated an association between hypertension and neurological complications, including alterations in consciousness, seizures, or convulsions; additionally, children with a history of hypertensive encephalopathy have shown similar lowered performance patterns on neurocognitive assessments as those with CKD alone (Trompeter, Smith, Hoare, Neville, & Chantler, 1982; Uysal, Renda, Saatci, Yalaz, 1990). In adults and children with ESRD, cognitive impairments have been linked to cortical defects associated with multiple infarcts (Lass, Buscombe, Harber, Davenport, & Hilson, 1999; Qvist et al., 2002). Animal models have also shown improved learning capacity on task acquisition for those with hypertension alone compared to those with hypertension associated with renal dysfunction (Widy-Tyszkiewicz, Scheel-Kruger, & Christensen, 1993). Given the

fact that hypertension is viewed by nephrologists as an important concern for pediatric patients with CKD (Swinford & Portman, 2004), it will be important to determine whether differences exist among the various aspects of attention as measured by Mirsky's neuropsychological model of attention when comparing these patients to their healthy peers.

CHAPTER III

METHODS

Participants

The current study examined the integrity of specific attention domains in 30 children with CKD, based on KDOQI Stages 2 through 5 (Table 1), compared with the performance of 41 typically-developing children. CKD was operationally defined as kidney disease of at least 3 months duration with an estimated glomerular filtration rate (eGFR) $\leq$ 75 mL/min/1.73m^2 or dialysis-dependency. All participants underwent comprehensive neuropsychological testing as part of a larger study examining neurocognitive outcomes in CKD, for which all participants were recruited to participate in accordance with the University of North Carolina Institutional Review Board procedures. Findings related to demographic and related variables for both samples can be viewed in Table 2.

CKD Group. Participants were enrolled in the CKD group through face-to-face recruitment with a research associate at the time of their pediatric nephrology clinic appointments. Enrollment occurred at the University of North Carolina Hospitals between 2002 and 2006. Inclusion criteria for this group comprised those participants with CKD (defined as eGFR $\leq$ 75 mL/min/1.73m^2) or dialysis-dependency for at least 3 months duration and chronological age between 6-18 years. Children were excluded from the CKD group if there was a history of kidney transplantation in the past or the presence of a comorbid condition associated with severe central nervous system

anomalies, such as a closed-head injury, Down syndrome, or Joubert syndrome. Participants engaged in 2-3 neuropsychological evaluations over one year, with testing occurring at baseline, optionally at 6-months, and 12-months after baseline. Results presented in the current study comprise baseline data only. Participants were provided with monetary compensation ($50) at the completion of each study visit.

Table 2.

Characteristics for the CKD (n = 30) and control (n = 41) groups.

	CKD	Controls
Chronological Age (years)	12.70 (3.32) (range: 6.45 – 19.04)	11.73 (3.36) (range: 6.11 – 18.94)
WASI Full Scale IQ***	90.70 (15.59) (range: 64 – 127)	113.51 (11.94) (range: 72 – 138)
% Caucasian*	50.0	73.2
% Female	46.7	43.9
SES***	2.93 (1.12)	4.15 (0.91)
Age of CKD onset (years)	5.11 (6.18) (range: birth – 16)	---
Duration of CKD (years)	6.40 (4.73) (range: 0 – 17)	---
% Hypertensive	50.0	---
% Anemic	30.0	---
Recent School Absences**	1.97 (2.74) (range: 0 – 9)	0.49 (1.39) (range: 0 – 5)

Notes. *$p < .05$; **$p < .01$; ***$p < .001$; Continuous variables presented as: Mean (Standard Deviation).

As shown in Table 2, participants in the CKD group (n = 30) consisted of individuals receiving maintenance dialysis therapy (n = 15) and those managed with conservative therapies (n = 15). The etiologies of CKD included obstructive uropathies/dysplasias (60%), glomerular disease (33%), and genetic disorders (7%).

Control Group. Children in the control group (n = 41) were recruited by posted fliers, newspaper advertisements, and electronic (e.g., e-mail, website) postings within the catchment area of the UNC Hospitals Pediatric Nephrology subspecialty clinic. Control participants were selected for study participation if there was no history of chronic health conditions, head trauma, seizures, frank neurological or psychiatric illness, developmental disorder, or current medication usage other than a multivitamin. Control group participants were demographically matched to the CKD patient sample on the variables of age, gender, race, and maternal education (collected by parent questionnaire). Demographic variables were collected for the control group, but medical variables were not collected so as to increase participation rates among volunteers. Control group participants were also provided with monetary compensation ($50) at the completion of each study visit in a similar fashion as the CKD group.

Procedures

All participants and their parent/guardian provided assent and consent prior to testing. Members of the CKD and control groups were tested as part of a larger study examining the neurocognitive effects of CKD and concurrent treatment modalities. Graduate students in the UNC School Psychology program were thoroughly trained in the use of instruments and study procedures before collecting data. Neuropsychological evaluations took place in either the General Clinical Research Center of UNC Hospital or at the Clinical Center for Development and Learning at UNC. Participants in the CKD group were tested as part of a clinical visit. Standard procedures were in place so that participants in the CKD group were tested prior to undergoing medical procedures (e.g., blood draws) or physical examinations to control for any potential negative reactions that

could invalidate test results. Participants in the control group only underwent neuropsychological testing and were not subject to any medical procedures.

The neuropsychological evaluations included an extensive child assessment measuring various neurocognitive domains, including attention. All neuropsychological instruments were administered in a standardized method in accordance with test manual guidelines. Parents were also asked to fill out several informal questionnaires requesting information on demographic and academic data, including race and socioeconomic status (given the associations with IQ; see Brooks-Gunn, Keblanov, & Duncan, 1996), previous grade retention, and recent school absences. Clinical variables, including disease severity (eGFR), duration of disease, age of onset, and comorbid diagnoses (e.g., anemia, hypertension) were obtained for participants in the CKD group from a physical examination with the patient's pediatric nephrologist. SES was defined by maternal education, which was nominally coded (1 = some high school, 2 = high school graduate or GED recipient, 3 = progress towards bachelor's degree or completed associate's degree, 4 = completed bachelor's degree, 5 = completed graduate or professional degree). Recent school absences were defined as number of absences in the last 30 days, or in the last month of the school if the visit occurred when classes were not in session.

Instruments

All participants received a variety of attention-related tasks. Measures were selected to align with the five-factor attention model posited by Mirsky and colleagues (Mirsky, 1987, 1989, 1996; Mirsky et al., 1991, 1995a, 1995b, 1999). These included selected variables from the Tower of London Test (TOL; Total Move, Total Execution Time scores), Gordon Diagnostic System (GDS; Total Correct, Mean Response Time,

Correct Variability scores), Keith Auditory Continuous Performance Test (ACPT; Total Correct, Correct Variability scores), Ruff Figural Fluency Test (RFFT; Perseverations Total score), and the Wide Range Assessment of Memory and Learning (WRAML; Finger Windows and Number/Letter subtest scores). Age-based standard scores (mean = 100, standard deviation = 15) were generated from available normative data when possible. When normative data were not available for particular age ranges (e.g., RFFT Perseverations, Keith ACPT Correct Variability scores), group means and standard deviations were generated from control group data. Higher standard scores reflect better performance in all analyses. As such, standard scores were reversed during conversions in instances when higher raw scores indicate poorer performance (e.g., TOL Total Move, Execution Time; GDS Mean Response Time; GDS/ACPT Correct Variability; RFFT Perseverations) to ease comparisons. The Wechsler Abbreviated Scale of Intelligence was also used as an estimate of overall intellectual functioning. All tasks were administered by trained examiners who were supervised by a child neuropsychologist.

Tower of London, Second (Drexel University) Edition (TOL). This problem solving task involves placing three beads on three pegs in a variety of configurations to match the pattern presented by the examiner. Several standard scores can be derived from the participant's performance including Total Test score, Initiation Time, Problem-Solving Time, Execution Time, Rule Violations, and Time Violations. Normative data are available for ages 6 years and above (Culbertson & Zillmer, 2001). Variables used for the current study included Total Test and Execution Time scores, both of which were reversed when converting from raw scores to standard scores to ease comparisons of the data.

Gordon Diagnostic System (GDS). The Vigilance portion of this task requires the participant to respond to specific visual stimuli (e.g., press the button when the number 1 followed by the number 9 is presented) from a series of numbers presented at a rate of about one per second. The GDS consists of three blocks of 15 possible correct responses over the span of 9 minutes. The task yields standard scores for the Total Correct, Correct Variability, Commissions, Commission Variability, Mean Response Time, and Response Time Variability. Normative data are available for ages 6 years and above (Gordon, 1986). Variables used in the current study included Total Correct, Mean Response Time, and Correct Variability scores, the latter two of which were reversed during standard score conversions.

Keith Auditory Continuous Performance Test (ACPT). This task of auditory attention requires the participant to raise his/her hand every time the word "dog" is read from a list of words. The list contains 96 total words and goes through 6 iterative blocks, each with a total of 20 presentations of "dog." This task yields standard scores for Total Correct and Total Error (omissions and commissions) scores. Normative data are available for children 6 years and above (Keith, 1994; Sykes, Douglas, & Morgenstern, 1973). Variables used in the current study included the Total Correct score and a Correct Variability score, which was calculated from the mean variance of correct responses by block for the control group.

Ruff Figural Fluency Test (RFFT). This task requires the participant to generate as many unique designs as possible by connecting two or more dots across a series of dot formations in a 60 second time period. There are five different trials, with distractors being present in two of the presentations. Standard scores include the number of unique

designs and the number of perseverations. Normative data are available for children and adolescents (Evans, Ruff, & Gualtieri, 1985; Vik & Ruff, 1988) as well as for individuals 16 years of age and older (Ruff, 1996). The Perseverations score was used in the current study. This variable was calculated for the entire sample using the mean number of perseverative responses for the control group, due to the fact that available normative data did not encompass the entire age range of this sample.

Wide Range Assessment of Memory and Learning (WRAML). The WRAML includes 9 different subtests that measure short-term verbal memory (Story Memory, Sentence Memory, Number/Letter), short-term visual memory (Picture Memory, Design Memory, Finger Windows), and new learning capabilities (Sound Symbol, Visual Learning, Verbal Learning). Subtest scores are provided as scaled scores (mean = 10, standard deviation = 3), and a General Memory Index can also be computed from the 9 subtests. Normative data are available for ages 6 through 17 years, 11 months (Adams & Sheslow, 1990).

The WRAML was administered and scored according to standardized procedures. However, three participants, one in the CKD group and two in the control group, were administered WRAML subtests despite being out of age range for this test (i.e., 18-19 years of age). Normative data for 17 year-olds were used for score conversions with these three participants given their close proximity in age to the normative sample. Additionally, all three participants were still in high school and therefore closely resembled the experiential profile of participants in the normative sample.

The Number/Letter and Finger Windows subtests were used for data analyses in the present study. The Number/Letter subtest is a task in which the participant is asked to

repeat a random mix of both numbers and letters verbally presented. The Finger Windows subtest measures the participant's attentiveness to a rote visual pattern by manually reproducing a demonstrated spatial sequence as the examiner points to increasingly longer series of locations found on a card. These two subtests are verbal and visual analogs of one another, in that both deal with immediate recall of discrete and non-meaningful information. Scaled scores from the Finger Windows and Number/Letter subtests were converted to standard scores for ease of comparison.

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI is built on the well-known Wechsler measures of global intellectual functioning. It was designed for ages 6 years through adulthood, and employs a fluid-crystallized model of intelligence (Wechsler, 1999). Four subtests comprise the WASI including Vocabulary, Block Design, Similarities, and Matrix Reasoning. All four subtests were administered to gain a brief IQ score.

Attention domains by Measurement Outcomes

Outcome measures from each of the above instruments were used to match onto attention domains in Mirsky's model. The exact measures used in Mirsky's factor analytic studies were used when available to the researcher and when that particular measure was appropriate to use with pediatric patients. When this was not the case, measures analogous to those used in Mirsky's model were employed. Each domain utilized two outcome measures to assess attention across the five domains of Mirsky's model. A breakdown of the distribution of outcome measures among the five domains in Mirsky's model of attention can be seen in Table 3.

Table 3.

Measurement variables organized by attention domain.

Attention Domains	Measures Used
Focus / Execute	- GDS Mean Response Time - TOL Execution Time
Sustain	- GDS Total Correct - ACPT Total Correct
Stability	- GDS Correct Variability - ACPT Correct Variability
Shift	- TOL Total Score - Ruff Perseverations Score
Encode	- WRAML Number/Letter subtest - WRAML Finger Windows subtest

Focus/Execute. To assess how participants concentrate attentional resources on tasks under timed conditions, screen out distractors, and respond rapidly to the demands of tasks, two variables from the previously described tasks were employed. Mean Response Time from the GDS and Execution Time from the TOL were the variables used to measure the Focus/Execute domain of Mirsky's model. These variables were selected due to the high degree of association between the task demands for both measures and those measured within this domain of Mirsky's model, in addition to a moderate internal consistency ($\alpha = 0.56$) with one another. Both tasks require participants to maintain their concentration, ignore distractions, and respond rapidly, which are the main aspects of the Focus/Execute domain in Mirsky's model.

Sustain. The GDS and ACPT Total Correct variables were used to measure participants' abilities to maintain attention to task over an extended period of time, which is the hallmark of the Sustain domain in Mirsky's model of attention. These variables were selected due to their similarity with variables historically used in Mirsky's model (i.e., total number of correct responses from the CPT) as well as a strong internal consistency ($\alpha = 0.65$) with one another.

Stability. In order to measure the degree of consistency of attentive responses over time, variables from the GDS and ACPT were also used to determine participants' stability of attention. The degree of variability among the three trial blocks on the GDS yield scores for Correct Variability, which determines the consistency of participants' visual sustained attention over the course of the task. Correct Variability on the ACPT among Iterations 1, 2, 3, 4, 5, and 6 provided an outcome analogous to GDS Correct Variability to measure the stability of auditory attention over time. These outcome measures were paired together because they are in line with those utilized in Mirsky's model and have a moderate internal consistency ($\alpha = 0.53$) with one another.

Shift. The ability to efficiently shift attention from one salient aspect of a task to another was measured across visual-spatial and visual-constructive domains. The current study first employed the TOL Total score to measure an individual's ability to shift attentive problem-solving strategies among 10 arrangements of beads on pegs. The RFFT Perseveration variable was also used to provide a measure of visual-constructive set-shifting as individuals attempt to avoid repeating similar designs within each of five trials. These measures are analogous to the set-shifting component of the WCST used in Mirsky's original model, and have been used previously in studies in which set-shifting

was measured (Gipson et al., 2006; Hooper et al., 2002). They also exhibited a moderate internal consistency ($\alpha = 0.49$) with one another in the current study.

Encode. The measurements of working memory capacity utilized for the current study included the Number/Letter and Finger Windows subtests from the WRAML. These two measures were selected in order to cover verbal and visual working memory abilities, respectively. These measures align with the suggestion of digit span tasks made in Mirsky's model of attention, and had a moderate internal consistency ($\alpha = 0.67$).

Preliminary Data Analyses

Prior to conducting statistical analyses, the domains within Mirsky's model of attention were calculated. Age-based standard scores (mean = 100, standard deviation = 15) were calculated from normative data for the following variables: TOL Total Move, Total Execution Time; GDS Total Correct, Mean Response Time, Correct Variability; ACPT Total Correct. Scaled scores (mean = 10, standard deviation = 3) from WRAML subtests (Finger Windows, Number/Letter) were converted to standard scores for ease of comparison. When normative data were not available (e.g., RFFT Perseverations, Keith ACPT Correct Variability scores), group means and standard deviations were generated from control group data to calculate standard scores for the entire sample. Standard scores were reversed during the conversion process when higher raw scores reflected poorer performance on certain variables (i.e., TOL Total Move, Execution Time; GDS Mean Response Time; GDS/ACPT Correct Variability; RFFT Perseverations), so that higher standard scores indicated better performance in all statistical comparisons. Once standard scores were generated for all variables, alpha coefficients were calculated as

reliability measurements to assess the internal consistency within each attention domain to determine if the selected measures were appropriate for use.

Preliminary analyses compared the CKD and control groups on the variables of gender, race, SES, and IQ scores to determine whether the groups differed systematically on any of these variables. If differences between the groups were evident on any of these variables with the potential to confound results, each was examined for its contribution to attention and then a decision was made whether to use it as a covariate in subsequent analyses. If no differences between groups were found, subsequent analyses were conducted without using any of these variables as covariates. However, chronological age was chosen a priori as a covariate for all subsequent analyses given the wide age range in the entire sample.

Research Questions, Hypotheses, and Data Analyses

Question 1

Do specific domains of attention in children and adolescents with CKD differ significantly from those measured in typically-developing children and adolescents?

Hypothesis 1

It was hypothesized that children with CKD would be at increased risk for attention problems when compared to a matched control group. Specifically, it was expected that the performance of children with CKD would be lower than the control group in the following attention domains: Focus/Execute, Sustain, and Encode. It was also hypothesized that the CKD group would exhibit similar performance to the control group on the Stability and Shift attention domains. Available research suggests negative

outcomes in specific domains of attention for children and adolescents with CKD (Fennell et al., 1990a, 1990b; Gipson et al., 2006; Qvist et al., 2002; Yount et al., 1998).

Data Analysis 1

Scores on the five attention domains posited by Mirsky were compared between the CKD and control groups using MANCOVA (chronological age as the covariate) and univariate procedures. Estimates of effect sizes were calculated using Cohen's *d* (Cohen, 1988), using standard definitions for small (d = 0.2-0.4), medium, (d = 0.5-0.7), and large ($d \geq 0.8$) effect sizes. SPSS was used to conduct all statistical analyses.

Question 2

Do pediatric patients with CKD differ significantly from typically-developing children in their observed proportion of attention problems? Specifically, does a higher proportion of pediatric patients with CKD evidence difficulties with attention one standard deviation or more below the mean (i.e., SS $\leq$ 85)?

Hypothesis 2

Existing research on neurocognitive outcomes in children with CKD has found evidence of increased prevalence of neurocognitive deficits in the CKD population (Duquette et al., 2007; Qvist et al., 2002). It was hypothesized that a higher proportion of children in the CKD group would demonstrate attention problems (SS $\leq$ 85) relative to the control group within several specific attention domains (Focus/Execute, Sustain, and Encode). It was also hypothesized that children in the CKD group would demonstrate similar proportions of problems on the Stability and Shift attention domains.

Data Analysis 2

The proportion of cases with attention dysfunction in the CKD and control groups was compared for each of the five attention domains using Pearson's Chi-square analyses in crosstabs in SPSS. An alpha level of .01 was used for these comparisons by utilizing a Bonferroni correction for the 5 analyses (i.e., .05/5).

Question 3

What functional- (e.g., recent school absences, IQ), family- (e.g., SES), and disease-related (e.g., disease severity, age of onset, duration of disease) variables predict attention domain scores?

Hypothesis 3

It was hypothesized that lower IQ scores, higher numbers of school absences, lower SES, earlier age of CKD onset, longer duration of CKD, more severe levels of CKD (i.e., lower eGFR calculations; NKF, 2002; see Table 1), and co-morbid diagnoses of anemia or hypertension would be associated with lower scores on all attention domains (Focus/Execute, Sustain, Stability, Shift, Encode). Furthermore, it was hypothesized that IQ scores, SES, and CKD severity (eGFR) would be significant predictors of all five attention domains within the proposed model of attention.

Data Analysis 3

A correlation matrix was constructed on CKD group data to examine the relationships among all measures, including intercorrelations among attention domain scores, IQ, recent school absences, SES, eGFR, age of CKD onset, duration of CKD, and anemia/hypertension status. Up to three variables with the highest degree of correlation with attention domains were included as predictor variables in separate regression equations for each of the five attention domains. A ratio of 10 cases for each variable

included in the regression equation was utilized to ensure statistical power and confidence in the regression analyses and subsequent regression weights.

CHAPTER IV

RESULTS

Preliminary Analyses

Reliability estimates were calculated among the ten variables selected for use in this study, and Cronbach's alpha coefficients suggested that the variables exhibited internal consistency within each attention domain (Focus/Execute, $\alpha = 0.56$; Sustain, $\alpha = 0.65$; Stability, $\alpha = 0.53$; Shift, $\alpha = 0.49$; Encode, $\alpha = 0.67$). Internal consistency for the all attention variables was also appropriate ($\alpha = 0.79$). Given these findings, the attention domains were calculated as described above by calculating the arithmetic mean of the two variables assigned to each attention domain.

Several t-tests were conducted to evaluate group differences between the CKD and control groups with respect to chronological age and IQ. For each ANOVA, the independent variable (i.e., disease status) included only two levels: CKD versus the control group. Pearson's Chi-square tests were run to compare the groups on the variables of SES, gender, and race.

Chronological age. Results from an independent samples t-test revealed no group differences on the mean age of participants at testing, $t(69) = 1.21$, $p = .23$. However, as mentioned previously, chronological age was used as a covariate in subsequent analyses given the wide age range of the entire sample.

Full Scale IQ. The CKD and control groups differed significantly in their overall levels of intelligence based on the Full Scale IQ score from the WASI, $t(69) = 6.99$, $p <$

.001. The mean score for the CKD group fell at the lower end of the average range (Table 2), indicating a slight downward shift in scores for the group as a whole. Because general intellect can be an important factor in the integrity of attention, IQ scores from the WASI were covaried in later analyses.

Socioeconomic status. A chi-square test revealed significant differences between the two groups on SES, $\chi^2 = 20.06$, $p < .001$. In general, the mean SES levels for both groups indicated that most of the mothers had achieved a high school degree and perhaps some post high school education/training. Because the Full Scale IQ score from the WASI and maternal education scores were moderately correlated ($r = 0.597$, $p < .001$), SES was not used as a covariate in subsequent analyses.

Gender and Race. A chi-square test indicated that the CKD and control groups were not significantly different in terms of gender distribution ($\chi^2 = 0.53$, $p = .82$). Gender was therefore not used as a covariate in subsequent analyses. The groups differed only slightly in relation to race ($\chi^2 = 4.01$, $p = .045$). Given the lack of effect of race on attention functions found previously in the literature (see Samuels et al., 1998, 1999), race was not used as a covariate in subsequent analyses.

Question 1

Do specific domains of attention in children and adolescents with CKD differ significantly from those measured in typically-developing children and adolescents? It was hypothesized that children with CKD would be at increased risk for attention problems when compared to a matched control group. Specifically, it was expected that the performance of children with CKD would be lower than the control group in the following attention domains: Focus/Execute, Sustain, and Encode. It was also

hypothesized that the CKD group would exhibit similar performance to the control group on the Stability and Shift attention domains.

Descriptive statistics, including means and standard deviations adjusted for age and IQ scores, for the CKD and control groups are presented in Table 4. Scores for the control group were arithmetically higher than those for the CKD group across attention domains. Visual inspection of the data indicated that mean scores for both groups on all attention domains were within one standard deviation of the overall mean.

Table 4.

Attention by group (CKD, n = 30; control, n = 41) and domain adjusted for age and IQ.

	CKD		Control			
	M	*SD*	*M*	*SD*	F-Tests	Effect Size
Focus/Execute*	94.67	11.43	99.73	8.51	4.58	0.50
Sustain*	94.37	16.24	103.30	14.83	5.80	0.57
Stability*	87.22	18.29	96.97	16.31	5.59	0.56
Shift	91.50	11.02	95.74	11.88	2.10	0.35
Encode***	88.67	9.38	99.47	10.13	19.61	1.07

Notes. $*p < .05$; $**p < .01$; $***p < .001$; Effect size presented as Cohen's *d*.

A multivariate analysis of variance (MANOVA) was performed to determine whether the CKD and control groups differed from one another on the five attention domains (Focus/Execute, Sustain, Stability, Shift, Encode). Chronological age and the Full Scale IQ score from the WASI were entered as covariates to control for between-group differences and possible confounding factors. Age was entered as a covariate variable to control for the effect of task demands by age across the wide age range in the entire sample. Using IQ scores as a covariate variable also helped to ensure that

differences could be attributed to group membership and not to overall intelligence. The domain means by group can be found in Table 4.

All assumptions necessary for MANCOVA were evaluated prior to running these analyses. To test for the assumption that the covariance matrices of the groups were equal, Box's M was examined and produced a non-significant result ($p = .59$). This suggested that the covariance matrices were not equivalent and could be pooled into one matrix. The data set was also inspected and analyzed to determine whether it met the assumptions of MANOVA set forth by Tabachnick and Fidell (2001). For the current study samples, the data were found to be univariately normally distributed and therefore no problems with multivariate normal distributions were anticipated. All assumptions related to linearity, homogeneity of regression, and the absence of multicollinearity and singularity were also met. The reliability of the covariates, chronological age and the Full Scale IQ from the WASI, were also found to be adequate. The adequacy of the Full Scale IQ score was confirmed by the psychometric properties of the WASI, including good reliability and validity. Additionally, two outliers were identified in the data set and were recoded to be within 3 standard deviations from the group mean using a Windsor procedure. This helped to ensure that error rates were not overinflated while still keeping these two data points in the analysis.

Pillai's trace (PT) for the MANCOVA revealed a non-significant interaction between the WASI Full Scale IQ and the groups, $F(5, 63) = 1.53$, $p = .20$, and between chronological age and the groups, $F(5, 63) = 0.72$, $p = .61$. This finding suggested that the MANCOVA could be interpreted for the attention domains. Results from the MANCOVA indicated that the CKD and control groups differed across attention domains

as evidenced by a significant Wilks' Lambda, $F(5, 63) = 3.32$, $p = .01$, $d = 0.83$. Follow-up univariate procedures indicated that the control group differed from the CKD group on the Focus/Execute, $F(1, 67) = 4.58$, $p = .04$, $d = 0.50$; Sustain, $F(1, 67) = 5.80$, $p = .02$, $d = 0.57$; Stability, $F(1, 67) = 5.59$, $p = .02$, $d = 0.56$; and the Encode domains, $F(1, 67) = 19.61$, $p < .001$, $d = 1.07$. The CKD and control groups did not differ significantly with respect to group comparisons on the Shift ($p = .15$, $d = 0.35$) domain.

Question 2

Do pediatric patients with CKD differ significantly from typically-developing children in their observed proportion of attention problems? Specifically, does a higher proportion of pediatric patients with CKD evidence difficulties with attention one standard deviation or more below the mean (i.e., SS $\leq$ 85)? It was hypothesized that a higher proportion of children in the CKD group would demonstrate attention problems (SS $\leq$ 85) relative to the control group within several specific attention domains (Focus/Execute, Sustain, and Encode). It was also hypothesized that children in the CKD group would demonstrate similar proportions of problems on the Stability and Shift attention domains.

The two groups were compared on each of the five attention domains using chi-square tests to determine whether the proportion of cases whose attention domain scores fell one standard deviation or more below the mean differed between groups, as shown in Table 5. The CKD and control groups differed in the frequency with which they experienced significant attention dysfunction on selected domains. The proportion of scores more than one standard deviation below the mean differed significantly between groups on the domains of Shift, χ^2 (1, $n = 71$) = 7.84, $p = .005$; and Encode, χ^2 (1, $n = 71$)

= 10.73, p = .001. The proportion of participants with attention dysfunction was similar between groups on the domains of Focus/Execute, χ^2 (1, n = 71) = 1.52, p = .22; Sustain, χ^2 (1, n = 71) = 2.46, p = .12; and Stability, χ^2 (1, n = 71) = 1.75, p = .19.

Table 5.

Proportions of participants with attention domain scores at least one standard deviation below the mean for the CKD versus control groups.

	CKD	Control
Focus/Execute	5/30 (17%)	3/41 (7%)
Sustain	9/30 (30%)	6/41 (15%)
Stability	10/30 (33%)	8/41 (20%)
Shift*	10/30 (33%)	3/41 (7%)
Encode**	13/30 (43%)	4/41 (10%)

Notes. *p < .05; **p < .01; ***p < .001

Question 3

What functional- (e.g., recent school absences, IQ), family- (e.g., SES), and disease-related (e.g., disease severity, age of onset, duration of disease) variables predict attention domain scores? It was hypothesized that lower IQ scores, higher numbers of school absences, lower SES, earlier age of CKD onset, longer duration of CKD, lower eGFR calculations, and co-morbid diagnoses of anemia or hypertension would be associated with lower scores on all attention domains (Focus/Execute, Sustain, Stability, Shift, Encode). It was also hypothesized that IQ scores, SES, and CKD severity (eGFR) would be significant predictors of all five attention domains within the proposed model of attention.

Correlations were derived among the attention outcome measures and the variables selected a priori (i.e., recent school absences, IQ, maternal education, disease severity, age of onset, duration of disease, comorbid diagnoses; Table 6). For all five of the attention domains (Focus/Execute, Sustain, Stability, Shift, Encode), three variables were significantly correlated, including WASI Full Scale IQ, SES, and eGFR (i.e., CKD severity). Recent school absences were negatively correlated with the Sustain and Stability domains. Age of CKD onset, duration of CKD, and having a comorbid diagnosis of anemia or hypertension were not significantly correlated with any attention domains. Variables that were correlated with the attention domains were then considered for inclusion in the regression equations. A maximum of three variables were selected for entry into each regression equation in order to maintain a 10:1 case to variable ratio, given that the CKD group consisted of 30 participants.

The three variables selected for the regression equations tapped the broad areas of general neurocognitive functioning (WASI Full Scale IQ), family characteristics (SES), and severity of disease (eGFR). Due to the exploratory nature of these analyses and the small sample sizes used in these regression equations, the results of the overall regression equations were not interpreted. Variables that predicted attention outcomes in the current CKD sample are discussed to provide future research with an initial model from which to work and test using larger data sets. As shown in Table 7, results indicated that no predictor variables emerged as significant for the attention domains of Focus/Execute, Sustain, or Shift. The regression equation for the Stability construct yielded the WASI Full Scale IQ as a significant predictor variable. Similarly, the WASI Full Scale IQ emerged as a significant predictor of the Encode construct.

Table 6.

Correlations among attention domains and predictor variables.

	Focus/ Execute	Sustain	Stability	Shift	Encode	School Absences	Full Scale IQ	SES	eGFR	Age of Onset	Duration of CKD	Hypertension	Anemia
Focus/Execute	1												
Sustain	0.59**	1											
Stability	0.50**	0.71**	1										
Shift	0.40**	0.10	0.17	1									
Encode	0.48**	0.48**	0.37**	0.47**	1								
School Absences	-0.19	-0.30*	-0.35**	-0.08	-0.10	1							
Full Scale IQ	0.45**	0.38**	0.39**	0.28*	0.56**	-0.29*	1						
SES	0.35**	0.29*	0.24*	0.26*	0.51**	-0.07	0.60**	1					
eGFR	0.39**	0.36**	0.33**	0.24*	0.51**	-0.49**	0.74**	0.53**	1				
Age of Onset	0.27	0.09	-0.15	0.19	0.30	0.30	0.04	0.30	-0.07	1			
Duration of CKD	-0.30	-0.16	-0.03	-0.24	-0.36	-0.23	-0.32	-0.45*	-0.25	-0.76**	1		
Hypertension	-0.05	0.21	-0.11	-0.12	0.03	0.24	0.05	-0.11	-0.10	0.03	0.01	1	
Anemia	-0.01	-0.34	-0.23	0.04	-0.20	-0.18	0.17	-0.03	-0.02	-0.04	0.15	-0.02	1

Notes: *$p < .01$; **$p < .001$

Table 7.

Regression equation coefficients by attention domain.

Attention Domain	Predictor Variables	Beta	t	Significance
Focus/Execute	WASI Full Scale IQ	.351	1.523	.140
	eGFR (CKD Severity)	.226	1.080	.290
	SES	.105	.575	.570
Sustain	WASI Full Scale IQ	.388	1.571	.128
	eGFR (CKD Severity)	.097	.430	.671
	SES	.057	.291	.773
Stability	WASI Full Scale IQ*	.556	2.256	.033
	eGFR (CKD Severity)	-.079	-.355	.726
	SES	-.038	-.196	.846
Shift	WASI Full Scale IQ	-.025	-.092	.928
	eGFR (CKD Severity)	.184	.740	.466
	SES	.138	.636	.530
Encode	WASI Full Scale IQ*	.497	2.053	.048
	eGFR (CKD Severity)	.092	.409	.686
	SES	.049	.247	.807

Notes: * $p < .05$

Additional Exploratory Analyses

Once the data analyses were conducted to address the research questions and associated hypotheses, several additional exploratory data analyses were executed to determine the presence of any trends in the data that could assist with hypothesis testing for a larger study sample. As such, the CKD group was subdivided into two groups, the

Mild/Moderate CKD group and the End-Stage Renal Disease (ESRD) group, to determine the effect of disease severity, or lack thereof, accounting for the CKD versus control group differences reported above.

Preliminary data analyses on the WASI Full Scale IQ scores indicated that the Mild/Moderate CKD group (M = 100.00, SD = 13.02) differed significantly from the ESRD group (M = 81.40, SD = 12.20), $F(1, 28) = 16.31$, $p < .001$. The WASI Full Scale IQ was therefore used as a covariate on the subsequent ANCOVA analyses. Visual analysis of the descriptive statistics indicated a trend in the data for poorer performance by the ESRD group in several domains (Table 8). However, due to the small sample sizes and high correlations between the WASI Full Scale IQ and each of the attention domains, the Mild/Moderate CKD and ESRD groups could not be adequately compared on the attention domains using the WASI Full Scale IQ as a covariate.

Table 8.

Attention by group (Mild/Moderate CKD, n = 15; ESRD, n = 15) and domain.

	ESRD		Mild/Moderate CKD			
	M	*SD*	*M*	*SD*	F-Tests	Effect Size
Focus/Execute**	88.32	12.33	101.01	5.70	13.08	1.32
Sustain*	87.19	18.56	101.54	9.55	7.09	0.97
Stability*	78.84	19.89	95.41	12.43	7.49	0.99
Shift	90.22	12.79	92.78	9.19	0.40	0.23
Encode*	85.33	10.56	92.50	6.48	5.02	0.82

Notes. *$p < .05$; **$p < .01$; ***$p < .001$; Effect size presented as Cohen's *d*.

Exploratory univariate analyses of variance (ANOVAs) were then performed to determine if a trend existed in the data suggesting that the Mild/Moderate CKD and

ESRD groups differed from one another on the five attention domains. Results from the univariate procedures indicated that the Mild/Moderate CKD group differed from the ESRD group on the Focus/Execute, $F(1, 28) = 13.08$, $p = .001$, $d = 1.32$; Sustain, $F(1, 28) = 7.093$, $p = .02$, $d = 0.97$; Stability, $F(1, 28) = 7.49$, $p = .01$, $d = 0.99$; and the Encode domains, $F(1, 28) = 5.021$, $p = .03$, $d = 0.82$. The Mild/Moderate CKD and ESRD groups did not differ significantly with respect to group comparisons on the Shift ($p = .53$, $d = 0.23$) domain.

To obtain a better understanding of the Mild/Moderate CKD and ESRD data, chi-square analyses were conducted to examine the proportion of children in each group who evidenced significant attentional impairment one standard deviation or more below the mean. Results from the chi-square analyses revealed that the Mild/Moderate CKD and ESRD groups differed significantly with respect to the proportion of children demonstrating significant problems on the Focus/Execute domain, χ^2 (1, $n = 30$) = 6.00, $p = .01$; the Sustain domain, χ^2 (1, $n = 30$) = 7.78, $p = .005$; and the Stability domain, χ^2 (1, $n = 30$) = 5.40, $p = .02$. Results approached significance for the Encode domain, χ^2 (1, $n = 30$) = 3.39, $p = .065$. The Mild/Moderate CKD and ESRD groups did not differ with respect to the proportion of cases evidencing attention dysfunction on the Shift domain, χ^2 (1, $n = 30$) = 0.00, $p = 1.000$ (Table 9).

Results from each of these exploratory analyses are to be interpreted with extreme caution and cannot be generalized beyond the current sample. Small sample size and lack of adequate statistical power prevent any such interpretation to be made. However, these findings may provide some preliminary evidence for the effect of disease severity

on attention in children with CKD. These factors related to disease severity should be considered by researchers when planning future studies.

Table 9.

Proportions of attention domain scores at least one standard deviation below the mean for the Mild/Moderate CKD versus ESRD groups.

	Mild/Moderate CKD	ESRD
Focus/Execute*	0/15 (0%)	5/15 (33%)
Sustain**	1/15 (7%)	8/15 (53%)
Stability*	2/15 (13%)	8/15 (53%)
Shift	5/15 (33%)	5/15 (33%)
Encode	4/15 (27%)	9/15 (60%)

Notes: * $p < .05$, ** $p < .01$

CHAPTER V

DISCUSSION

The current study examined whether children with chronic kidney disease (CKD) demonstrated impairments in specific domains of their attention functioning relative to a group of their typically-developing peers. Attention is arguably one of the most vital neurocognitive functions of childhood in that it factors into a child's ability to acquire, understand, and retain learned information in social and educational environments. Because of this importance, attentional dysfunction could predispose a child to difficulties in other areas as well, including his or her academic performance or interpersonal relatedness. Due to the fact that children with CKD evidence executive function deficits (Gipson et al., 2006), an in-depth understanding of the effects of pediatric CKD on the integrity of attention processes was warranted.

The current literature on neurocognitive outcomes for school-age children with CKD suggests a number of findings indicative of cognitive dysfunction. A number of these studies have collectively revealed a trend for some generalized deficits in cognition (Bawden et al., 2004; Brouhard et al., 2000; Lawry et al., 1994; Mendley & Zelko, 1999; Qvist et al., 2002). Interpreting the available findings related to specific neurocognitive functions in children with CKD has been problematic due to the significant improvements made in medical and pharmacological interventions (Gorman, 1995; Grantham-McGregor, 1995; Halterman et al., 2001; Lande et al., 2003; Marsh et al., 1991; NKF, 2002). However, the consensus among contemporary studies examining

memory and executive functions in pediatric CKD is that these neurodevelopmental abilities should be monitored over time for any possible deficits (Fennell et al., 1990; Gipson et al., 2006; Mendley & Zelko, 1999; Qvist et al., 2002). Taking the literature on attention in adults with CKD also into consideration (Yount et al., 1998), there is sufficient evidence to suggest the possibility of specific weaknesses in aspects of attention for children with CKD.

Although previous research has examined general and specific neurocognitive functions in pediatric patients with CKD, no known research has targeted specific domains of attention in children with CKD. The current study attempted to address this gap in the extant literature by comparing the performance of children with CKD on five attention domains to that of a comparison group comprised of typically-developing children. Strengths related to this study include use of an empirically supported model of attention and a study design using a case-control comparison, which assists in drawing conclusions about the effects of CKD on attention outcomes outside of the influence of demographic factors. Multiple measures of attention also were used to construct the attention domains. The text below discusses the results of the current study by examining the obtained results with the hypotheses established a priori. Possible explanations for the results, limitations of this study, and potential areas for future research follow.

Question 1

Do specific domains of attention in children and adolescents with CKD differ significantly from those measured in typically-developing children and adolescents? It was hypothesized that children with CKD would be at increased risk for attention problems when compared to a matched control group. Specifically, it was expected that

the performance of children with CKD would be lower than the control group in the following attention domains: Focus/Execute, Sustain, and Encode. It was also hypothesized that the CKD group would exhibit similar performance to the control group on the Stability and Shift attention domains.

The proposed hypotheses were partially supported by the obtained results. Group differences were obtained on the MANCOVA analysis, and follow-up univariate procedures indicated that the control group differed significantly from the CKD group on several attention domains. Specifically, the control group obtained significantly higher scores than the CKD group, even after controlling for differences in IQ and age, on the Focus/Execute, Sustain, Stability and Encode attention domains. No significant group differences were evident on univariate follow-up procedures with regards to Shift attention domain.

Question 2

Do pediatric patients with CKD differ significantly from typically-developing children in their observed proportion of attention problems? Specifically, does a higher proportion of pediatric patients with CKD evidence difficulties with attention one standard deviation or more below the mean (i.e., SS $\leq$ 85)? It was hypothesized that a higher proportion of children in the CKD group would demonstrate attention problems (SS $\leq$ 85) relative to the control group within several specific attention domains (Focus/Execute, Sustain, and Encode). It was also hypothesized that children in the CKD group would demonstrate similar proportions of problems on the Stability and Shift attention domains.

In order to rule out the potential effects of individual participants' scores confounding the group comparisons in research question #1, the proportion of children who scored one standard deviation or more below the mean on each attention domain was compared by group. The obtained findings again partially supported the proposed hypothesis, as results indicated that the CKD and control groups differed with respect to the proportion of participants who fell one standard deviation or more below the mean on the Shift and Encode attention domains. The range of participants in the CKD group falling one standard deviation or more below the mean on attention domains (17% on Focus/Execute, 43% on Encode; Table 5) was similar in frequency to findings in at least one previous study (Qvist et al., 2002) in which the prevalence of generalized attention deficits was estimated to be approximately one-fourth of the study sample.

Additional Exploratory Analyses for Questions 1 & 2

The division of the CKD group into the Mild/Moderate CKD and ESRD groups allowed for comparisons across disease severity groups. Children in the ESRD group were found to have significantly lower IQ scores than the Mild/Moderate CKD group. Univariate comparisons of the two groups on attention domains without using IQ as a covariate indicated that the two groups differed significantly on the Focus/Execute, Sustain, Stability, and Encode attention domains (Table 8). Children across these two severity groups also differed in the proportions of clinically significant attention problems on the Focus/Execute, Sustain, and Stability domains, with the ESRD group having a higher proportion showing evidence of attention dysfunction (Table 9). The implications for these findings suggest that children with the most severe levels of CKD (i.e., kidney failure, ESRD) should be monitored closely in their overall neurocognitive

development, certainly with regard to their generalized intelligence and perhaps also with regards to specific neurocognitive functions such as attention skills.

Interpretation for Questions 1 & 2

Results from the current study provide some of the most comprehensive findings to date on the attention functioning of children with CKD. Although based on a relatively small sample, the obtained results further illustrate the emerging concerns related to the integrity of generalized and specific neurocognitive dysfunction for children with CKD. This study demonstrated lower performance within several specific domains of attention, including focused/timed concentration, sustained attention, stability of attention across time, and poorer encoding of information retrieved through attention processes, for children with CKD relative to typically-developing peers. These findings were present while controlling for the generalized effects of age and intelligence. In this regard, these findings are consistent with the available literature suggesting the presence of subtle cognitive deficits in children with CKD (Gipson et al., 2006; Hart et al., 1983; Qvist et al., 2002; Slickers et al., 2007).

It is important to consider that while the CKD differed significantly with respect to performance on the four attention domains mentioned above, children in the CKD group performed generally within the average range as a group. Additionally, in contrast to the slight downward shift in specific domains of attention (e.g., Focus/Execute, Sustain, Stability, and Encode) in the current study, the CKD group did not differ from the control group with regard to shifting from one salient aspect of a stimulus to another (Shift). This finding suggests a possible functional strength for children with CKD with respect to these brain-based functions, particularly with respect to frontal lobe integrity.

Keeping in line with previous research suggesting limited to no group differences and mostly intact functioning related to attention (Fennell et al., 1990a, 1990b; Mendley & Zelko, 1999; Qvist et al., 2002), this finding on the Shift domain suggests that numerous factors related to CKD could affect performance on attention-related tasks. Previous findings on memory, executive functions, and clinical predictors of neurocognitive dysfunction with this same sample are consistent with the obtained results on shifting and sustained attention, lending additional support to this finding (Gipson et al., 2006; Slickers et al., 2007).

Several explanations are possible for the findings related to attention domains as well as the proportion of attention dysfunction for these first two research questions. First, the main explanation for the obtained findings could be related to measurement questions. It is quite possible that attention outcomes related to CKD during childhood were extremely difficult to measure in this sample due to the evolution of frontal lobe functioning occurring during the school-age and pre-teen years. Since the mean age for the CKD sample was approximately 12-13 years of age (Table 2), the process of identifying attention problems through direct measurement could have been problematic given the varying trajectories of frontal lobe development at these wide age ranges. As such, the effects of CKD on attention may lie dormant until the teenage years when adolescents are presented with tasks and experiences in high school requiring sophisticated attention and executive functioning. Although significant differences were obtained when chronological age was controlled for in the current study, it will be necessary to replicate these findings with a more targeted age range of participants in order to generalize the findings. In this sense, extraneous factors such as task demands as

a function of developmental stage, treatment adherence, later effects of CKD, and small sample sizes are important considerations to make when interpreting the obtained differences for these specific attention domains.

Another possible explanation for group differences in specific attention domains could be due to morbidity effects related to CKD severity. In this regard, it is within reason that children presenting to their pediatric nephrologist with the most severe levels of CKD (i.e., kidney failure; ESRD) may be more urgent candidates for a kidney transplant. Additionally, previous research has shown that children with CKD can experience improvements in specific neurocognitive functions, including attention, following a kidney transplant (Mendley & Zelko, 1999). Because this study focused only on children and adolescents with CKD who had not previously undergone a kidney transplant, the remaining patient sample from the current study could potentially represent a subset of CKD patients with adequate medical and neurocognitive outcomes at the time of study participation. Similarly, patients who required kidney transplants prior to participation in this study could also potentially represent a contrasting subset of CKD patients that experience a higher incidence of neurocognitive dysfunction, but were not included in this study. Therefore, a large-scale study that can capture a large proportion of pediatric patients with CKD may capture more generalized attention problems due to the potential morbidity effects.

An additional explanation related to morbidity is that children with kidney failure (ESRD) in this study may have been monitored more closely because of the severity of their illness. By this line of thinking, the extent of CKD severity may have alerted the pediatric nephrologists responsible for these children's medical care to discuss the

potential risks for neurodevelopmental deficits with parents and teachers. Although this is merely speculation, any extra intervention not accounted for in the study design, such as special education services, could have mediated outcomes related to attention in this study. Analyzing physician notes related to informal clinical monitoring of neurocognitive development could provide additional insight into this potential explanation.

Regarding the inconsistency in group differences for the proportion of attention dysfunction by group, one possible explanation could be that children with CKD evidence differential impairments in their attention across the age range. This suggests that specific attention impairments could emerge at different time points for each child, particularly when academic task demands increase and students are increasingly responsible for independently maintaining attention to preserve their own success in the classroom. In addition, children with CKD may receive more monitoring and educational supports as part of their medical care, in an effort to intervene with attention problems when they first emerge. This explanation would provide much positive support for early/preventive intervention services following the diagnosis of CKD.

The issue of treatment adherence is also of importance when discussing attention in children with CKD. However, data related to adherence to medical and pharmacological regimens were not available for analysis with this sample. Previous literature has discussed the pathophysiological mechanism by which CKD leads to progressive waste product accumulation in the body, which precedes uremia-induced cognitive difficulties (Gipson et al., 2004). Therefore, the issue of adherence seems to be a potentially confounding variable that could warrant further investigation in future

studies. Although the use of a typically-developing control group allowed for comparison between the CKD group and their demographically-matched peers, it is potentially feasible that children with complicated forms of CKD could have more erratic patterns of adherence, due in part to the complicated nature of their treatment (i.e., dialysis, medications, dietary restrictions) regimens. The ability to accurately detect difficulties with treatment adherence through laboratory findings would be necessary to monitor the association with specific neurocognitive problems. Serial assessments with in-depth analysis of laboratory findings beginning at CKD diagnosis could also provide a better analysis of neurocognitive functioning as a byproduct of adherence longitudinally.

An additional explanation for the inconsistent findings across attention domains in this study deals with the relatively small sample size afforded by studying such a specific chronic illness of childhood. The ability to recruit a larger sample through a multi-site study could produce stronger findings with greater statistical power. Furthermore, a larger sample could allow for in-depth analysis of children with CKD by disease severity group with the use of a comparison group (i.e., Mild/Moderate CKD vs. ESRD vs. Control groups) that could potentially reveal other subtle differences in the data.

In general, these findings suggest that the presence of CKD during childhood may result in subtle, specific deficits in certain domains of attention. Results indicated that these weaknesses in specific domains of attention were disproportionate for children with CKD, and were evident above and beyond the contribution of general intelligence. However, a number of other factors, including disease severity, treatment adherence, task demands by age, and previous intervention and available supports may play a significant

contributing role in determining whether attention deficits are manifested for a child with CKD.

Question 3

What functional- (e.g., recent school absences, IQ), family- (e.g., SES), and disease-related (e.g., disease severity, age of onset, duration of disease) variables predict attention domain scores? It was hypothesized that lower IQ scores, higher numbers of school absences, lower SES, earlier age of CKD onset, longer duration of CKD, lower eGFR calculations, and co-morbid diagnoses of anemia or hypertension would be associated with lower scores on all attention domains (Focus/Execute, Sustain, Stability, Shift, Encode). It was also hypothesized that IQ scores, SES, and CKD severity (eGFR) would be significant predictors of all five attention domains within the proposed model of attention.

Interpretation for Question 3

Although the small sample size for this study ruled out any broad generalizations related to the findings in research question #3, this portion of the current study attempted to determine whether variables could preliminarily predict attention outcomes for children with CKD. The development of such a model to predict attention outcomes in school-age children with CKD could provide pediatric nephrologists with a means of identifying children at risk for this specific neurocognitive deficit.

The general trend in the data was for small-to-moderate positive correlations to exist among several predictor variables (WASI Full Scale IQ, SES, eGFR scores) and attention domains (Focus/Execute, Sustain, Stability, Shift, and Encode). This data suggested that higher scores on these attention domains were related to higher IQ scores,

higher levels of SES, and higher filtration levels in the kidneys (i.e., lower CKD severity). These three variables reflected the broad categories of child characteristics (IQ), family characteristics (maternal education), and disease characteristics (CKD severity). Moderate negative associations were also evident between the number of recent school absences and the Sustain and Stability attention domains, indicating that fewer school absences were associated with higher scores on these attention domains. It was interesting to note that age of CKD onset and duration of CKD were not found to be associated with any of the attention domains.

Results from the regression equations showed WASI Full Scale IQ score to be a significant predictor of the Stability and Encode attention domains. WASI Full Scale IQ was also found to approach significance with respect to predicting scores on the Focus/Execute and Sustain domains. However, no other variables were significant predictors of the attention domains.

The findings from this study were in slight contrast to the findings with this sample by Slickers and colleagues (2007), in which no associations were evident between clinical predictor variables and generalized attention data from the Gordon Diagnostic System. From a face validity perspective, it was surprising that CKD severity was not a significant predictor for any of the attention domains, particularly given previous findings indicating CKD severity to be significantly associated with IQ and memory scores (Slickers et al., 2007). The lack of predictive value for age of CKD onset and duration of CKD on attention domains was also surprising, although this lack of association may reflect the tendency for patients to present initially to their pediatric nephrologist with already severe disease (Slickers et al., 2007). As has been suggested by other researchers

(Slickers et al., 2007), this situation would make the date of CKD onset less reflective of the point at which reduced renal function actually occurred, thereby reducing the predictive value of these variables. Nonetheless, the current findings represent the first of its kind with respect to clinical predictors of specific attention domains with a sample of pediatric patients with CKD.

Overall, the obtained data were among the first to date that focused on identifying potential risk factors for attention dysfunction in children with CKD. Future research must examine potential predictors of attentional dysfunction more carefully so as to assist in creating a model of cumulative risk. Perhaps larger sample sizes can help to better parse out predictor variables with respect to the impact of attention functioning.

Limitations

Although the current study provided contemporary findings on subject matter that has not received adequate attention in the extant literature, certain limitations inherent to this study exist and are discussed as follows in an effort to guide future research. First and foremost, the small sample size for the CKD group was to be expected given the specificity of inclusion/exclusion criteria for a chronic illness of childhood. As such, the number of CKD group participants (n = 30) precluded any broad generalizations from the data and limited the amount of within-group analysis that could occur. Additionally, the matching of demographic variables for the comparison group ideally would have been more accurate. Although the CKD and control groups did not differ with respect to chronological age, gender, or race, the variables of child IQ and SES differed significantly between groups. Future research could address this limitation and better match the groups through several recruiting methods, including the use of sibling-

matched controls, the collection of more detailed information gathering during recruitment to ensure proper matching, and/or increased recruitment in low- and middle-class neighborhoods.

From a measurement perspective, several specific issues were also evident in the current study. First, as discussed previously in the introduction, parsing apart attention from executive functions and memory is difficult from both theoretical and data-gathering perspectives. The degree of overlap among these three constructs is debatable, but undoubtedly present to a certain degree. Additionally, the age at which the majority of participants were enrolled in the study corresponds with the time frame for developmental trajectories of frontal lobe impairments. Therefore, the previously discussed factor of task demands by age is another limitation that could have precluded finding more severe or quantitatively more group differences on attention domains. With regards to research design, this study examines each child's performance at baseline – one data point – and therefore cannot account for situational/environmental factors that could have hindered or enhanced a child's performance on the day of study participation. Furthermore, longitudinal tracking of attention outcomes over time in these participants is also difficult given that many of the instruments used were designed for use with school-age children only.

Future Research

The current study examined a topic that has gone largely unaddressed in the area of CKD research. Current findings suggest that certain aspects of attention may be vulnerable to the presence of CKD during childhood, with factors such as general intelligence and disease severity potentially impacting the degree of attentional

impairment. These results also suggest that CKD may not global deficit in attention, although additional research is required to confirm these findings and deal with the limitations of the current study. Future research should set out to establish large sample sizes through multi-site or multi-center collaboration in order to allow for more extensive analysis of predictor variables through regression equations. This process would allow for the development of a predictive model of attentional outcomes in children with CKD, giving pediatric nephrologists a valuable tool to guide collaborative care and better monitor the neurocognitive needs of this population. Future research would also benefit from gathering extensive information regarding the available services and educational/social supports in the child's community, so as to learn more about the formal and informal interventions that could potentially mediate outcomes. Additionally, the use of attention-specific parent and teacher questionnaires would also be helpful in providing reliable observations of the child's typical attention functioning on a daily basis in different settings (i.e., home and school). Longitudinal follow-up could also provide a better perspective of the development of attentional impairments over time as the task demands of middle and high school bring subtle neurocognitive deficits to the observation of parents and teachers.

Future research should also focus on the intervention needs for children with CKD with regard to educational supports and the role taken on by psychologists and/or educational support staff. In this regard, researchers should attempt to clarify the question of function versus etiology in this population with regards to attention. By doing so, it will provide parent, teachers, and professionals with specific information on the reason these children need intervention, as well as the target of said interventions.

Psychologists will likely play the role of assessor through periodic monitoring via neuropsychological assessments, and may also play the valuable role of conveying developmental expectations relative to the neurocognitive functioning of the child with CKD.

With regards to classification in the schools, future research should also weigh the positive and negative aspects of providing educational support services to children with CKD broadly under a general medical heading (e.g., Other Health Impaired – OHI), with a secondary classification for any cases of specific neurocognitive deficits (e.g., LD for specific academic delays). This consideration could help parents and teachers to better document their child's educational and social-emotional needs at school. This consideration for multiple special education classifications could also facilitate serving each child's unique educational needs related to extended periods of absenteeism for medical visits, fatigue related to chronic illness, and emerging psychoeducational deficits secondary to CKD progression. In this sense, this pursuit could potentially provide an interventional and classification framework aimed at providing the most appropriate services to children with CKD. This process could also produce the secondary benefit of educating teachers and staff as to the specific areas of cognitive difficulty and the nature and nuances of CKD.

Conclusions

Children with CKD can potentially evidence a variety of general and specific neurocognitive deficits. Due to a lack of findings on this topic in the available literature, the current study compared the attention functioning of school-age children with CKD to a group of typically-developing controls. Significant differences on group means were

revealed between the CKD (n = 30) and control (n = 41) groups on the Stability and Encode attention constructs. No other group differences emerged on the Focus/Execute, Sustain, and Shift attention constructs. The CKD and control groups did not differ with respect to the observed incidence of significant attentional dysfunction. Exploratory analyses with a subdivided CKD group suggested that the end-stage renal disease (ESRD, i.e., kidney failure) group had a higher incidence of significant attentional impairments on the Stability and Encode attention constructs. IQ scores and maternal education were found to be positively correlated to a moderate degree with attention outcomes, while disease severity and recent school absences were negatively correlated to a moderate degree with attention outcomes. Additionally, IQ scores were a significant predictor of the Stability and Encode attention constructs. No predictors emerged for the Focus/Execute, Sustain, or Shift attention constructs.

Taken together, the results of this study implicate subtle and specific attentional dysfunctions, particularly in stability of attention over time and encoding of information, for children with CKD. As a whole, these findings may suggest a chronic vulnerability of higher-order neurocognitive functions in children and adolescents with CKD. This raises questions regarding the integrity of the structure and function of frontal and prefrontal brain regions in the pediatric CKD population, with specific concerns for neurodevelopmental insults associated with disease severity, the age of onset, and/or the duration of kidney disease. These findings also raise questions regarding how and when neurodevelopmental trajectories of targeted brain regions may be affected, and suggest that these brain regions may be vulnerable to the effects of uremia and the accumulation of waste products that are associated with CKD.

In sum, the current findings should assist in beginning to target attention for neurodevelopmental surveillance within this population. It will also be critical for children with CKD to receive close developmental surveillance and monitoring of these functions. Through long-term, systematic follow-up, the issue of attention functioning in CKD may be addressed in reference to the timeliness, type, and response to various individualized interventions for these children.

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