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Cognitive Impairment in Chronic Kidney Disease: Are oculomotor tests an effective detection marker?

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This thesis is submitted in fulfilment of the requirements for the degree of Master of Science at Lancaster University

Declaration

This thesis is entirely my own work and has not been submitted in full or in part for the award of a higher degree at any other educational institution.

No sections of this thesis have been published. One poster presentation was made and this is detailed in Appendix 1.

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Abstract

People with chronic kidney disease (CKD) are at increased risk of developing cognitive impairment (CI) compared to the general population, in fact, it has been estimated that 60% of people with CKD are cognitively impaired.[1] Despite this high percentage, there is no adequate screening process for the detection of CI in this high risk population.[1] Lack of a suitable diagnostic tool therefore allows impairment to go unchecked, increasing the risk of dementia evolution.[2]

Previous research has demonstrated that oculomotor tasks may be advantageous over traditional neuropsychological measures for detecting CI in early Alzheimer's disease, specifically uncorrected error rate in the anti-saccade paradigm.[3, 4] This particular measure examines individuals' inhibitory control, self-monitoring and executive functioning abilities. Consequently, these facets of cognitive functioning are commonly found to be impaired in people with CKD.[1]

This study aimed to investigate the effectiveness of uncorrected error rate in the anti-saccade paradigm as a detection tool for CI in people with CKD. In a cross-sectional design, 44 CKD patients and 25 controls completed the anti-saccade task and a neuropsychological battery that assessed global ability, working memory, and executive function.

The prevalence of CI was evaluated, as was the anti-saccade task's ability in predicting the extent of cognitive impairment. Subsequently, it was found that uncorrected error rate was significantly higher in those with advanced CKD requiring haemodialysis, as was prevalence of CI according to scores in the neuropsychological battery. Furthermore, uncorrected error rate was predictive of deterioration in some cognitive abilities, namely visuospatial memory, verbal working memory, and verbal inhibitory control with small to moderate effect sizes.

These results support previous research in that those with advanced CKD are more likely to have CI when compared to the general population.[1] They also represent the first exploration

of the anti-saccade paradigm as a monitoring tool for CI in CKD, and indicate that the anti-saccade task has the potential to act as a cost and time-effective means of periodically assessing certain domains of cognition in people with CKD. Despite this, further work using the anti-saccade paradigm longitudinally and in larger population sizes is needed to confirm its use in clinical practice.

1. Introduction

1.1 Chronic Kidney Disease

CKD is broadly described as abnormal kidney structure and/or function for three months or longer. While this definition is simplistic, it encompasses a large group of heterogeneous disorders. In developed countries the most common causes for CKD are chronic health conditions.[5] Although there may be difficulties in giving a precise diagnosis, it is believed that the main causative aetiologies for CKD in the developed world are diabetic glomerulosclerosis and hypertensive nephrosclerosis.[6] CKD associated with diabetic glomeruloscerlosis accounts for 20-40% of CKD cases and hypertension is linked to 5- 25% of prevalent cases.[6] The remainder of CKD cases are due to congenital malformations, glomerular and neoplastic diseases. On the other hand, in developing nations, the majority of CKD can be attributed to infectious diseases, e.g. malaria, schistosomiasis and hepatitis B, rather than chronic disease. However, the World Health Organization[7] has reported that the incidence of CKD due to chronic vascular disease is increasing in developing countries.[7] This illustrates the global increase of vascular disease as a cause for CKD. Overall, CKD is the twelfth highest cause of mortality and the seventeenth highest cause of disability worldwide.[8] The risk of developing CKD increases with age which is specifically problematic in the developed world due to the demographical trend of an aging population.[6] It has been estimated that 7% of the population worldwide have a CKD diagnosis but it is likely that the 'true' percentage of CKD in national and international populations is higher.[9] Although routine laboratory tests are sufficient in detecting CKD, a proportion of people are undiagnosed as the CKD is asymptomatic in its early stages. Moreover, CKD symptoms are non-specific creating the risk of misdiagnosis or a delay in seeking medical advice. The typical presenting complaint of CKD is the feeling of fatigue and weakness with subsequent decreased quality of life. This combination and other CKD signs and symptoms are due to accumulation of urea, a metabolic waste product. As CKD progresses, there is failure to

eliminate urea and other nitrogenous metabolic end products. As such, there is an increased concentration of urea in the blood which is a clinical marker of uremic syndrome in CKD. As aforementioned, significant symptoms include fatigue and weakness, but there are many other clinical manifestations affecting multiple systems at different CKD stages. These are shown in the below table along with secondary diseases associated with CKD.

Table 1 Signs, symptoms and secondary diseases associated with chronic kidney disease[6, 10]

System affected by uraemia	*Clinical Features*
Cardiovascular	Accelerated systemic atherosclerosis, hypertension, uremic pericarditis, heart failure (secondary to pulmonary oedema)
Gastrointestinal	Nausea, anorexia, vomiting, diarrhoea
Central nervous system	Confusion, coma, uremic encephalopathy (severe uremia)
Peripheral nervous system	Restless leg syndrome, limb cramps, paraesthesia, neuropathic limb pain, weakness
Haematological	Haemostasis disorders causing pulmonary and peripheral oedema, secondary normochromic normocytic anaemia causing breathlessness, pallor and lethargy
Endocrinology	Infertility, sexual dysfunction,
Skin	Dryness, pruritis, pigmentation
Bone	Renal Osteodystrophy; hyperparathyroidism causing bone pain and eventual deformity. Osteomalacia.
Biochemical	Metabolic acidosis, hyperkalaemia causing cardiac arrhythmia, hyperphosphatemia, hypocalcaemia
Immunity	Decreased response rate to vaccinations, more prone to infections

CKD is both progressive and irreversible and the above symptoms often intensify in severity and frequency in proportion with declining kidney function.[10] While drug treatments are available to slow progression of disease and treat accompanying complications, everyone with a diagnosis of CKD is at risk of developing end stage renal disease (ERSD). This is the final

stage of CKD where little can be done to manage complications and renal replacement therapy (transplant or dialysis) is needed. Fortunately, few cases are first diagnosed in this late phase and staging classifications exist so earlier CKD can be accurately diagnosed and managed, halting progression into ERSD. The UK National Institute of Health and Clinical Excellence[11] (NICE) have adopted the Kidney Disease: Improving Global Outcomes (KDIGO)[12] Work Group's classifications, and recommend that they are combined to assess severity of CKD.[11, 12] These taxonomies organise CKD into stages based on the biological markers Glomerular Filtration Rate (GFR) and Albumin: Creatinine ratio (ACR). The staging systems are based on these markers and are illustrated in the figures 1 and 2 below.

Figure 1. Stages of chronic kidney disease according to GFR value. Adapted from KDIGO guidelines[12]

Classification of renal impairment according to GFR in CKD (NICE Jul 2014 and KDIGO Jan 2013)		
Stage	GFR (ml/min per 1.73m^2)	Interpretation
1	>90	Normal GFR, with other clinical evidence of renal damage e.g. abnormalities on imaging techniques or in urine samples (white blood cells, protein, blood)
2	60-89	Evidence of mild renal damage with reduced GFR
3A 3B	45-60 30-44	Moderate renal damage. Other clinical evidence not needed.
4	15-29	Severe renal damage
5	<15	Renal failure
ERSD	<15 or requiring transplant/dialysis despite GFR value	

Figure 2. Chronic kidney disease categoris according to albuminuria. Adapted from KDIGO guidelines.[12]

Category	Urine Albumin Excretion Rate (AER) (mg/24 hours)	Urine Albumin to Creatinine Ratio (ACR) (mg/mmol)	Urine ACR (mg/g)	Interpretation
A1	<30	<3	<30	Normal /mild levels
A2	30-300	3-30	30-300	Moderate levels
A3	>300	>30	>300	Severely increased levels

While these staging classifications are concise, it is important to identify where those with ESRD and early CKD belong within this context. Firstly, CKD is 'officially' diagnosed when GFR falls below 60ml/min per 1.73m^2.[12] Thereafter, uremic symptoms begin to appear.[6] However, some renal pathologies do not impact GFR values and CKD is diagnosed when there are other obvious renal abnormalities detected in urine samples (protein, inflammatory markers, blood) or by imaging methods.[12] The latter category, ERSD, is a permanent and irreversible decline in kidney function, which is fatal in the absence of kidney transplant or dialysis. ERSD includes all individuals diagnosed with stage 5 CKD, those requiring haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) regardless of GFR value. While ERSD in itself is profoundly debilitating, dialysis treatment is both time consuming and invasive. The only definitive 'cure' for ERSD is renal transplant, which is a physically and psychologically demanding process for the patient. Moreover, renal transplant may ultimately result in graft rejection from an already limited supply of organ donors. Not all ERSD patients are candidates for transplant due to co-morbid conditions meaning they are reliant on dialysis as life sustaining treatment. The psychological repercussions of these diverse and chronic issues may manifest as anxiety and/or depression. Particularly for people receiving HD this may seem unsurprising, as the procedure is physically invasive and time consuming. Furthermore, it is disruptive to vocational and social roles and requires modification of lifestyle, e.g. restriction of fluid and salt intake, strict medication regime, etc.

Those with earlier CKD may also be required to make unwanted lifestyle alterations in order to defer treatment with dialysis. While these psychological implications for people with CKD have been historically recognised, a new issue that appears to be emerging is cognitive dysfunction in all stages of CKD. Current research attempts to clarify the causes for CI; associated comorbidities, psychosocial issues and the direct physical effects of CKD have all been hypothesized to contribute in some manner. CI is at risk of progressing to dementia; an irreversible, progressive and permanent decline in cognitive functioning, which may be accompanied by subjective disruptions in mood. [13]While the exact mechanism remains unclear, it has been shown that a dose-dependent relationship between extent of disease (GFR) and severity of CI exists.[2, 14-16]

1.2 Cognitive Impairment: Pattern in CKD populations, potential causes and risk factors

Cognitive impairment is an acquired abnormality in two or more domains of cognitive functioning. This may include impediment of memory, language, perceptual motor abilities, executive functioning, attention or speed of processing.[13] Mild cognitive impairment (MCI) is a term that is used when CI becomes clinically detectable but the impairment does not affect an individual's daily functioning.[13, 17, 18] CI and MCI are heterogeneous conditions with a number of subtypes that are at risk of developing into a dementia syndrome.[18] Dementia is the 'umbrella' term used to describe the grouping of aetiologies that cause irreversible multi-domain cognitive impairment that impact an individual's daily functioning.[17, 19] It has been estimated that 60% of dementia cases are due to AD in the general population, as opposed to 'pure' vascular dementia which accounts for 20% of cases. (20) Alternatively in CKD populations, vascular and mixed pattern (AD and vascular dementia) are the most commonly occurring subtypes of dementia due to the high proportion of causative/ concurrent vascular comorbidities.[1] Given this, it is unsurprising that the label of 'vascular'/ 'dysexectuive'

MCI/CI has been used synonymously with CI in CKD rather than 'amnesiac' MCI which is associated with AD.

Each of these subtypes can be described as 'prodromal' to either AD or vascular dementia. Vascular CI resembles vascular dementia in that symptoms are 'stepwise' in their onset and progression with fluctuating severity.[17, 21] Typically, it is viewed that executive functioning, attention, psychomotor speed and mood are affected in vascular MCI while global ability, short term and working memory abilities are spared. By comparison, 'amnesiac' MCI is sometimes appropriated with AD whereby lapses in episodic memory are common, performance in working memory tasks are poor and global abilities are intact.[13, 17, 19] Although these terms aid identification of those at risk of dementia evolution, it is accepted that the boundaries between amnesiac and dysexecutive MCI are not always readily distinguishable.[19] It is likely that these defined terminologies represent separate locations on a MCI/CI spectrum which is reflective of both specific and complicated CI aetiologies. Particularly in CKD, dysexecutive impairment is likely to be commonly observed due to the prevalence of vascular disease as aforementioned. However, it has been found that performance in working memory tasks have also been adversely affected in CKD populations, and that some exhibit patterns suggestive of amnesiac MCI independently of global ability.[22, 23] Again, this is reflective of a complex and multifactorial cause of CI. Vascular disease is one facet of CI in CKD and should be considered in context with other potential CI causative factors that are associated directly with uraemia, CKD treatment and psychological implications.

1.3 The Vascular Hypothesis: The kidney and brain

People with CKD are more likely to have comorbid cerebrovascular disease or a neurodegenerative disorder in comparison to the general population.[24] The pathological link mediating this association is strongly believed to be the pathogenesis of small vessel disease.

People with CKD have increased exposure to traditional and non-traditional risk factors for vascular dementia, as shown in figure 3.

Figure 3. Vascular risk factors in chronic kidney disease. As adapted from Bugnicourt et al[25]

Traditional	Non-traditional
• Diabetes Mellitus • Hypertension • Aging • Hypercholesterolemia	• Chronic inflammation (due to uraemic toxins) • Oxidative stress

Therefore, in CKD populations there is believed to be a 'mirroring' of any vascular damage that may be present in renal arteries in cerebral arteries also. This concept was first identified by Ito et al. in their 'strain vessel' hypothesis.[26] This theory is becoming increasingly supported by CKD research, as it highlights the haemodynamic and physical properties the kidneys and brain share; both are low resistance organs exposed to a high-volume blood flow. Subsequently, identical pathological processes occur in both renal and cerebral arteries as they are caused by the same aetiological factors. Exposure to traditional vascular risk factors such as aging, diabetes mellitus, hypertension and hypercholesterolemia induces atherosclerosis, calcification and eventual hypo-perfusion in renal and cerebral arteries. [26-28] The additional exposure to non-traditional risk factors further increases cerebrovascular disease risk, and therefore risk of vascular MCI.[25] For example, as shown in figure 3, uremic toxicity and oxidative stress cause inflammation universally within all blood vessels as CKD progresses.

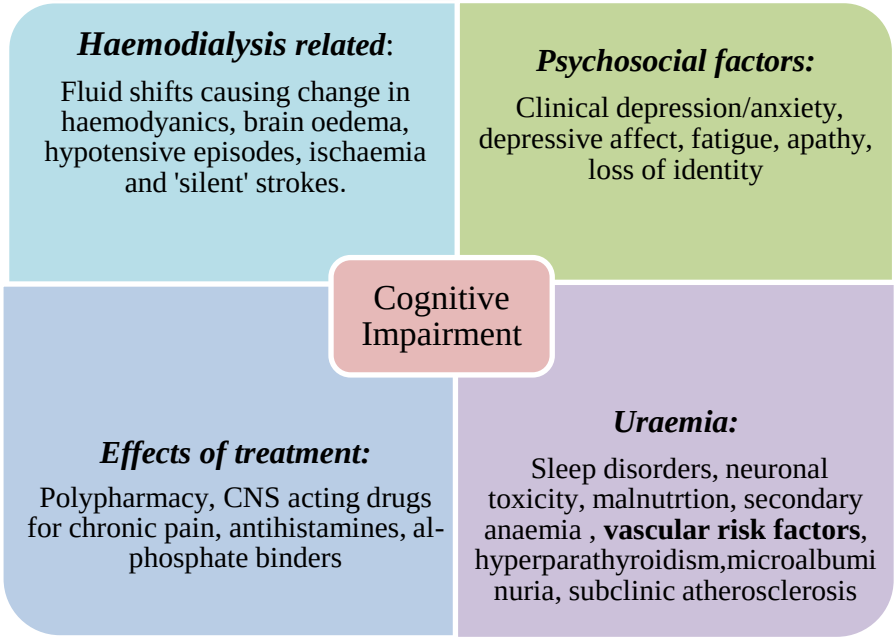
Long term inflammation from CKD causes the regulatory processes of all arteries to become deficient. This induces 'accelerated' atherosclerosis in vasculature independent of predated vascular disease.[23] As most people with CKD have comorbid hypertension or diabetes, the effect of this pre-existing vascular disease combined with uremic associated damage causes premature 'arterial aging' with subsequent ischaemia and calcification of blood vessels.[10] Unless these pathological changes are treated, they are at risk of progressing to cerebrovascular disease (stroke, or transient ischaemic attacks) in CKD populations. Therefore, it is unsurprising that the relative risk for stroke is six times more common for people with stage 5 CKD when compared to age-matched members of the population and people who have a stroke are twice as likely to develop dementia compared to the general population.[29] Significantly, there is a growing proportion of subclinical cerebrovascular disease in subcortical circuitry within CKD populations. [25, 30] The prevalence of which appears to be concentrated in HD subgroups. A number of studies examining this relationship have been carried out in both patient groups with consistent results.[31-33] For example, two magnetic resonance imaging (MRI) community studies found that the severity of subclinical vascular disease positively correlates with stage of CKD and acts as an independent risk factor for CI. One was a longitudinal study that used the mini mental state examination (MMSE), a relatively insensitive measure of cognitive functioning, with verbal fluency tasks.[32] The other was a cross-sectional study that used the Stroop task as its primary measure of CI.[33] While these neuropsychological batteries are small, the results these studies convey support the trend that some executive functions (verbal fluency, inhibition of pre-potent responses) are impaired in CKD. Additionally, they support the theory that the clinical pattern of CI in CKD somewhat resembles that in people with early vascular dementia and stroke. The longitudinal study examining this relationship also allows inferences about causality to be made. However, cerebrovascular disease is not the sole cause of CI in CKD and there are other confounding factors at play. Other community-based studies have shown that CI occurs in CKD independent of vascular disease status and have identified other confounding factors that require further discussion.

1.4 Psychological factors: depression, anxiety and quality of life

As has been shown in the previous sections, CKD is a complex disease with a number of symptoms and secondary complications that require an intricate and often invasive management plan. Naturally, the symptoms of CKD and its treatment are not always easily understood by people who receive a diagnosis. This may cause a disruption in individuals' perceived self-concept and self-esteem.[34-36] The effect of this, as with other chronic illnesses, may lead to a depressive episode or exacerbation of pre-existing depression.[37] In particular, people requiring HD may feel a loss of autonomy, as the opportunity for self-management decreases and the input of health professionals becomes central to disease treatment. Moreover, haemodialysis is time consuming as the standard dialysis regime for ESRD is three hour sessions four times per week. This interferes with vocational roles and may cause some people to identify as a 'patient' with symptoms, rather than a multi-faceted and productive individual. For those in earlier CKD stages, there may be a 'fear of dialysis' which can become a source of anxiety and long term psychological distress.[35] Depression and anxiety in CKD and HD populations is associated with an increased number of hospitalizations, co-morbid illnesses, lower perceived quality of life and CI.[38] Only a handful of studies have attempted to examine the relationship between depressive affect and CI in CKD populations, particularly in HD groups.[37, 39] For example, Agganis et al[39] found that HD participants with depression (16.6% of 241 participants), diagnosed by the Centre for Epidemiological Studies Depression Scale (CED-S) had significantly poor performances in measures of executive function and psychomotor speed (Trails A and B, digit symbol coding and block design.)[39] Typically, impairments in these areas are commonly seen in adults with later-life depression without CKD.[40, 41] The causality for the relationship between depression and CI in the general population is the subject of frequent debate and is likely to be bi-directional to a degree. However, other factors are at play when considering the effects of depression and anxiety on cognitive functioning in CKD. Subclinical vascular disease is a confounding factor

as it has been known to be linked to both CI and depression in older adults.[40] Additionally, fatigue and sleep disorders occurring resultant of CKD can cause apathy.[42, 43]This in turn may affect individuals' scores in cognitive assessments creating a false positive result which is not reflective of actual cognitive abilities.[17] Additionally, while many patients may not be formally treated for depression, it is likely that the prevalence of depressive and anxious affect is underestimated in CKD populations.[1] The physical indicators of depression and anxiety may often be overlooked as CKD patients often experience similar symptoms as would manifest in clinically typical depression, such as sleep disorders and nausea which prevents eating.[36] The thought processes associated with depressive affect predominate over physical symptoms, causing low mood, reduced self-esteem and fatigue. This combination is likely to cause 'sub-syndromal' depression.[43] Low mood and anxiety coupled with a perceived lack of control may cause some individuals receiving haemodialysis to experience a sense of hopelessness.[35, 44-46] In turn this may induce feelings of a lower quality of life, propagating depressive and anxious affect. Naturally, this combination may impact speed of processing, decision making, other facets of executive functioning and eventually global cognition. With this aspect and other potential causes of CI in CKD having been discussed, the current research identifying the components of CI affected by CKD and their measurement should be examined more closely. While it is outside the scope of this thesis to discuss all potential causative factors in detail, it is crucial to mention the numerous factors associated with the development of CI in CKD as shown overleaf.

Figure 4 Summary of factors impacting cognitive function in chronic kidney disease[25, 47]



It is important at this juncture to discuss the cognitive domains and abilities this combination of pathological factors affects, and subsequently the empirical research that illustrates this. The next section will aim to define and outline these affected abilities; executive function, working memory, and inhibitory control.

1.5 Executive Functioning

Executive function (EF) is the most commonly cited cognitive domain that is impacted negatively in people with both early CKD and ESRD. [1, 2, 38] While it is widely agreed upon that EF is a component of 'metacognition', it is lacking a universal definition. However, there appears to be a consensus that EF involves processes that allow planning, formation of goals, the ability to execute goals effectively, including the ability to adapt behaviour in novel situations so that goals can be achieved.[48, 49] There is also a lack of clarity as to whether or not EF is a unitary construct; some researchers agree that EF encompasses a number of

separable higher order processes (including other cognitive domains), others argue that there is a singular underlying mechanism for all aspects of EF, i.e. goal neglect.[50-53]

Many researchers support and have elaborated upon Alexander and Stuss'[51] model of EF as it identifies the specific interlinking components that are needed for EF and the processes that constitute these.[48, 51, 54] These components are as follows; attentional control, which involves inhibitory control (also considered as a separate domain/primary EF), the ability to self-regulate (monitor performance and correct where inappropriate) and maintain selective attention. Information processing is a separate component, which requires fluency; the withdrawing of relevant systematic clusters from working memory, and psychomotor speed which is the ability to extract information quickly and correctly for accurate and high-quality output.[54] The third component cognitive flexibility relies on the ability to rapidly switch between task-instructions, divide attention and create new strategies when required, (i.e. 'update') Lastly, goal-setting incorporates the ability to plan actions in advance, and constantly 'update' these plans based on newly formed concepts. This account of EF has been frequently cited as it outlines how activities of daily function decline in executive dysfunction.[53, 54] For example, those with poor attentional control recurrently make procedural mistakes, inability to process information adequately causes slowed reaction times etc. It should be noted that although these components have been described in a way that simultaneously distinguishes them from each other, but also identifies how they are functionally interlinked. Other reviews have highlighted this and in particular emphasize that some pathways are shared between EF and working memory and inhibitory control.[48, 55]

As aforementioned, inhibitory control was mentioned as process which is needed for attentional control, despite being considered a cognitive domain in its own right. Working memory is also widely accepted as a separate independent cognitive domain, even though it is listed above as a process comprising the attentional control, information processing and cognitive flexibility components of EF. For example, Miyake et al.[55] found that inhibition and working memory were distinguishable from other core executive functions (namely

shifting), but that all three moderately correlated with each other. This suggests that there may be at least some common underlying pathways between these abilities, despite them appearing to be distinct from another. The following sections describe these two constructs in more detail.

1.6 Working Memory

Working memory (WM) describes a limited capacity mental workspace that temporarily stores and manipulates information in a readily retrievable manner for a very brief timeframe (ranging from a few seconds to several minutes.)[56-59] It has been proposed that WM acts as an interface between individuals' initial perception, long term memory stores and subsequent action.[60] The most psychologically developed account of this construct is Baddeley and Hitch's[56] multi-component model of working memory. This conceptualization has supplanted previous basic 'stage' models describing short-term memory as an uncomplicated storage facility that serially liaised with long-term memory.[61] This model consists of four components: 1. A slave system known as the phonological loop, which stores auditory information short term and reinforces this through 'rehearsal'. 2. A second slave system known as the visuospatial sketch pad which stores visual information short term. 3. The central executive, which is a managerial component that selectively guides the manipulation, and storage of information received from both of the slave systems while maintaining this information for retrieval. 4. The episodic buffer, a third slave system and a recent addition to this model, creates, integrates and stores different types of information to form retrievable 'episodes', which allows for multi-modal storage and gives individuals a sense of timing and chronological order. [56, 62]

It should be noted that it is the central executive component that differentiates Baddeley's model of WM from short term memory. It is because of this component that WM is considered an integral part of executive functioning, as it allows for stored information to be

selectively used for planning, reasoning and dealing with abstract ideas.[56] Similarly, it should be noted that other researchers cite more complex functions as being central to WM over storage ability. For example, Oberauer et al.[63] proposed that WM constantly processes old and new information to replace pre-existing ideas and concepts in long-term memory (i.e. 'updating' which is involved in EF) which contributes to individuals' intelligence level. Likewise, Engle et al.[64] and Cowan[65] have proposed that WM is a system of long-term memories which need to be sufficiently 'activated' at a certain threshold to be processed and maintained by limited-capacity attentional processes. These memories are usually activated in a goal-directed context, highlighting the importance of personal motivation and interference control in WM functioning. Although these theoretical positions represent only a handful of numerous WM theories, however, they all have one common feature; working memory capacity (WMC).

WMC refers to the maximum amount of meaningful information that can be held in WM at a given time.[58] This brief definition does not only refer to how many items can be held in WM, but also how effectively WM functions.[66] Effective WMC involves attention being exclusively focused on relevant information in the context of goal-achievement despite interference. Some researchers also refer to this ability as 'executive attention'.[66, 67] Current research suggests that individuals with a larger WMC can more easily maintain top-down control processes, so attention can be focused on multiple and diverse task instructions compared to those with a low WMC.[68, 69] A key component hypothesized to be involved in preserving WMC and preventing it from being inundated is inhibitory control. Consequently, some researchers argue that inhibitory control determines WMC thereby making it an independent cognitive construct.[55, 70] The relationship this component of cognitive control has with EF and WM is outlined below.

1.7 Inhibitory Control

The overall role of inhibition in the context of cognitive and behavioural control has been defined as "the stopping or overriding of a mental process, in whole or in part, with or without intention" by MacLeod [((71)p5)] Through empirical research, three main types of inhibition have been identified[(72)]:

1. Suppression of a pre-potent (a dominant, but inappropriate) response
2. Filtering of non-task relevant information from entering and 'cluttering' WM workspace.
3. Ignoring and subsequently removing information from WM that is not task-relevant, but previously was (known as 'pro-active' interference).

Suppression of pre-potent responses is the component of inhibitory control that is most clearly associated with intentional suppression and executive functioning.[(73)] This form of inhibitory control is intentional and involves overruling automatic and habitual motor/ behavioural responses where they occur in a context requiring controlled responses in a goal-oriented situation. Empirical research suggests that the underlying neuropsychological mechanism for this type of control is centred around the competition between controlled and pre-potent mental signals.[(74, 75)] Representations for both of these responses are initiated when faced with a task, and the response which is more strongly reinforced and maintained (pre-potent or controlled) is subsequently performed. The remaining two types of inhibitory control are not considered to be wholly conscious and are more commonly linked to WM by researchers, in particular their relationship with WMC.[(70)]

The latter conceptualizations of inhibition are hypothesized as mechanisms that control content that enters WMC. However, there is a distinct difference between these two components of inhibition which should be clarified. Successfully filtering task irrelevant information, or 'resisting distractors' is the ability to refrain from engaging with, or resolve any interference from the external environment which contradicts current task instructions.[76] These distractors are presented concurrently with information needed to perform a task. The last form of inhibition differs from this. 'Proactive interference' describes prior, learned task-relevant instructions which have subsequently become irrelevant.[76] When the 'new' instructions fail to be maintained in WM and the old instructions are followed, this is referred to as an 'intrusion error'.

Although WMC and inhibitory exist as discrete functioning constructs and there is evidence that one can decline independently of the other, there is growing support for the hypothesis that decline in mechanisms of inhibitory control contribute in part to reduced cognitive performance; irrelevant information is not filtered, consuming limited WMC and therefore allowing other processes involved with EF and WM (manipulation of information, goal achievement) to attend to and process irrelevant information.[3, 77] In this context, it is hypothesized that effective inhibitory control contributes to the successful conscious attentional control of behaviour, as it allows for task-relevant information to be stored in WMC and maintained without interference by executive operations.[76]

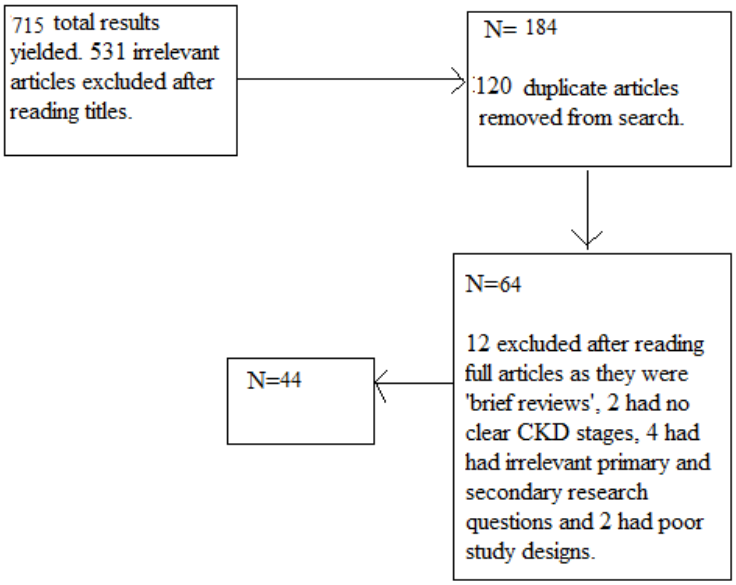
Again, it should be stressed that there is evidence suggesting that these three cognitive domains outlined in these sections can function discretely.[55, 78] However, they also share a synergistic relationship in certain situations. Namely, in tasks that require simultaneous planning, inhibition of procedural/learned responses and monitoring of errors so goals can be achieved effectively and efficiently.[66] In order to understand more fully which of these constructs are most affected in CKD, a literature review has been carried out below. The review was also carried out in order to investigate the presence the dose-dependent relationship between extent of CI and stage of CKD. This is significant to investigate as the

ability to identify earlier and subtler symptoms of CI is a key feature needed in a screening/monitoring tool.

1.8 Literature examining CI in CKD: trends and patterns

A search was made of the databases PubMed, PsycINFO, Academic Search Complete and MEDLINE in August 2016. These studies from both peer reviewed and non-peer reviewed journals were included in order to gain a fuller understanding of the nature and prevalence of CI in CKD. Only APA descriptor index terms were entered in to these databases: 'chronic kidney disease' AND 'cognitive impairment'. For studies to be included in the review, their primary or secondary research question had to explore the association between CKD and CI; risk factors, pattern of CI or the graded relationship. To begin with, studies were excluded after their titles were read and deemed to be clearly irrelevant. Thereafter, the remaining studies' abstracts were read, or the full text to decide if they were relevant. Studies without clear definitions of CKD categories based upon or similar to the KDIGO guidelines were excluded. Similarly, all of the studies had to include at least one validated neuropsychological measure to be included in the review. After these limits were applied, 42 studies were identified in total from database searches; 30 cross-sectional studies and 12 longitudinal studies. Additionally, no Cochrane review of empirical research of CI in CKD currently exists, however, two systematic reviews were published in 2012 and 2016 which analyse current empirical research studies which are included in the narrative below.

Figure 5. Flow chart depicting stages of study selection



1.8.1 Methodology and participants

A list of the studies included in this review are shown in Appendix 2. Of the 30 cross sectional studies included, seven were 'community-based', whereas 23 studies recruited specifically from CKD populations; nine recruited exclusively from HD groups, eight from pre-dialysis CKD groups, five from both HD and pre-dialysis populations and one comparing outcomes in a transplant population versus an ESRD population.[2, 22, 23, 37-39, 79-103] Nine of the longitudinal studies were community based, two recruited from HD populations and one compared cognitive performance in an ESRD group pre- and post-transplant.[15, 86, 104-113] The mean follow-up periods of these studies ranged from eight months to seven years. The total number of participants in all studies was 61,440; 1,553 were receiving HD, 8,366 were non-HD CKD, 50,282 were recruited from 'community studies' where the proportions of participants with CKD were not clearly established, 77 were participants who has successfully undergone renal

transplant and 1,162 non-CKD 'control' participants. Sample sizes ranged from 18 to 23,405 participants. Three of the included studies included a power equation or stated that appropriate calculations had been carried out to ensure an adequate number of participants were tested to give the study power of 0.8.[88, 99, 111] The mean age of participants with CKD was 57.3 years, with the ages of participants ranging from 18 to 86 years. There was also a wide range of psychometric tests used, batteries ranged from one to 19 measures. The most commonly utilised tests were those assessing global ability and EF/WM which are identified below.

1.8.2 Psychometric tests: Global cognition

27 studies in total administered tests of global cognition; 17 cross-sectional and 10 longitudinal studies.[2, 15, 37-39, 79-82, 84, 85, 87-91, 94, 98, 99, 102, 105, 106, 108-113] The most commonly used measures were the Mini-mental state examination [114] , referred to as the 'MMSE', (15 studies) and the Modified mini-mental state examination[115] , referred to as the '3MS' (10 studies).[2, 15, 37-39, 79-81, 84, 85, 87-90, 94, 99, 102, 105, 108-113] The remainder of studies used the six item cognitive screen test[116] (6-CIT), the Montreal cognitive assessment[117] (MoCA), and the cognitive screening interview for dementia[118] (D-CSI).[80, 82, 90, 91, 98, 106] A summary of these measures is shown in table 2. Three cross-sectional studies calculated global 'composite' scores from the raw scores of psychometric tests measuring other domains, rather than using a direct measure of global ability.[22, 83, 101]

Table 2 Summary of global measures used in cognitive impairment in CKD literature

Test	Description	Specificity/sensitivity	Test re-test reliability	Detection of MCI/ dementia
3MS	Incorporates original MMSE, assesses long term memory, category fluency, delayed recall and abstract thinking in addition to 30 point MMSE.	85-90/83-94[119]	68-77[120]	Discriminative between MCI and dementia
MMSE	30 point task assessing orientation, language, short term memory recall, visuospatial abilities and attention.	87/69[119] (sensitivity 18 for MCI)[117]	48-65[120]	Renowned for having poor sensitivity/specificity and test-retest reliability.
MoCA	30 point task assessing short term memory recall, language, verbal fluency,visuospatial abilities, executive function (planning, inhibitory control), sustained attention and working memory	50/87[121]	91[121]	Used for detection of MCI and dementia
6-CIT	6 item screening tool scored out of 28 points. Assesses orientation, short term memory recall.	100/79[121]	No published data available.	Cut-off point (10/11 points) suggestive of MCI. Discriminates between levels of CI/dementia
D-CSI	Mainly used for cross-cultural studies. Involves separate interviews with affected individuals with CI and informants.	87/83[118]	79[118]	Not validated in secondary healthcare settings

1.8.3 Psychometric tests: Executive functioning and working memory

Measures of EF/ tasks reliant on WMC were used more frequently than measures of global cognition. Overall, 33 of 41 studies utilised at least one measure of EF, the most commonly used being the Trails making B task[122] (TMT-B); 23 cross-sectional and three longitudinal studies.[2, 22, 23, 38, 39, 79, 81, 84-88, 90, 92-97, 99, 101, 102, 104, 105, 113] 16 studies also utilised the digit span task[123] and 12 utilised the digit symbol substitution task.[22, 38, 80, 83, 86, 88-93, 96, 97, 99, 101, 102, 104, 107, 113, 123] Other alternative measures that were used are shown below in Table 3.

Table 3 Summary of commonly used measures of executive function and working memory tasks in chronic kidney disease[48]

Test	Description	Component of EF	Other concepts
Trail making test part B	Connect 25 encircled numbers and letters in sequence. Time taken to complete task is recorded	Set shifting, planning, inhibition	Scanning and tracking
Stroop test[124]	Participant reads aloud the colour of ink that different colours are written in. Number of words vary. Time and number of errors are recorded.	Inhibition, attentional control	Working memory, Psychomotor speed Sustained attention
Digit Symbol Substitution	Participant is given a list of 9 digit-symbol 'matching' pairs. In a given time they must match a series of symbols to the correct corresponding digit.	Attentional control, planning, set shifting	Scanning and tracking
Wisconsin card sorting test[125]	Cards with different colours and numbers of shapes are presented to the participant. The participant has to 'match' one of the cards	Set shifting, inhibition attentional control	Working memory

	with a set according to an unknown rule which changes throughout the testing.		
Digit span (reverse)	Examiner reads aloud a sequence of numbers which becomes progressively longer. Participant immediately repeats sequence. Done in forward and reverse sequence. Reverse sequence mainly associated with EF while forward sequence is associated with working memory	Attentional control, inhibition	Working memory (phonological), psychomotor speed
Spatial span[123] (reverse)	Examiner taps out sequences on corsi blocks which becomes progressively longer. Participant has to immediately imitiate. Done in forward and backward sequence. Reverse sequence mainly associated with EF while forward sequence is associated with working memory	Attentional control, inhibition	Working memory (visuospatial), psychomotor speed
Phonemic and Semantic fluency tasks[126]	The phonemic verbal fluency task requires participants to list as many words beginning with a specific letter in one minute. The semantic fluency task requires the listing of as many words in a given category in a minute, e.g. animals.	Verbal fluency, attentional control	
Clock-drawing test[127]	Examiner instructs participant to draw a clock face illustrating a specific time. The examiner then draws a clock depicting the	Planning, attentional control	

	same time and participant is asked to copy their diagram. Types of errors shown in the drawings are then documented , e.g. distortions, substitutions, omissions etc.		

Executive dysfunction/ impairment in working memory was not consistently defined in the studies overall. For example, some studies defined participants as having dysexecutive MCI if they scored between one to two SD below the mean of controls' test scores in executive neuropsychological measures.[38, 88, 90, 99] Alternatively, other studies utilised variable defined cut-off scores specific to individual psychometric tests. For instance, in the TMT-B some studies described dysexecutive MCI as taking longer than 180 seconds to complete the task.[87, 95] Whereas other studies defined dysexecutive CI as taking more than 300 seconds to complete the task.[39, 87, 105]

1.8.4 Overview of results

Overall, only one of the studies (a longitudinal community-based study) did not find any significant associations between CKD and CI.[105] The remaining studies found that cognitive ability was generally poorer in CKD participants compared to control populations, community-dwellers without CKD and published norms of cognitive tests. As global cognition and certain executive functions (inhibition, set shifting) were the most commonly assessed, it is unsurprising that the remaining studies with exception to the above reported dysfunction in at least one of these areas, in addition to impairments in working memory, attention and language. These findings are considered below in conjunction with findings from systematic reviews.

1.8.5 Definition of Cognitive Impairment in the literature

Firstly, it should be highlighted that there was variability in what was defined as cognitive impairment among study participants. It should be noted that one of the systematic reviews identified this methodological issue.[128] A majority of studies had defined 'cut-offs' to delineate CI in individual measures used; seven cross-sectional studies of 30, had no clear definition of CI, and rather was classified as CKD and HD participants having a statistically significantly lower neuropsychological performance level than controls.[79, 80, 89, 91, 93, 100, 102] 11 of the studies defined CI as between one to two standard deviations below the mean scores obtained by age, sex and education matched controls.[38, 83, 84, 88, 90-92, 95, 99, 101, 103] Some further categorised the impairment as 'mild', 'moderate', or 'severe' and documented whether CI was amnesiac or non-amnesiac, and single-domain or multi-domain impairment.[23, 38, 88, 99]

Others used defined diagnostic cut-off scores that are commonly used for validated measures within in the general population, e.g. MCI constituted as <80 in the 3MS and <23 in the MMSE.[15, 87, 105, 109, 111] Some studies used alternative cut-offs to already established scores, for example, one study defined MCI as 26 points in the MMSE rather than 23 points.[102] Studies utilising the most common measure of executive functioning, the TMT-B, displayed the most variability when assessing participants' scores. Three cross-sectional and one longitudinal study used the standardized measure of >300 seconds taken to complete the task as representative of CI.[2, 39, 87, 105] One cross-sectional study used the time of >180 seconds to diagnose CI.[95] The remainder had either no formal cut-off, incorporated the time taken to complete the measure 'composite' score, or compared the mean taken to complete the TMT-B in controls as a reference point and established CI as between one to two S.D below this in CKD participants.[22, 23, 38, 79, 81, 83-86, 88, 90, 92-97, 99, 101, 102, 104, 113] Despite this lack of consistency, nine of twelve longitudinal studies had established what constituted a clinically significant

decline in follow-up testing so trends could be easily identified, for example, two points in the MMSE and 6-CIT and six points in the 3MS.[15, 86, 104-106, 109, 111-113] Despite this, on an aggregate level there was a significant amount of evidence supporting that people with CKD are more at risk of developing CI than those without as shown below.

1.8.6 Discussion of results

Longitudinal studies

Two studies (one with HD participants and one community study) found a clinical decline in the MMSE after a year was more common in CKD participants than controls and that this remained statistically significant after adjustment for demographic and other confounding variables.[109, 111] While the results of these studies may be limited due to the use of a single insensitive measure with poor test-retest reliability, one large community based study (3034 participants) supported these results by reporting that 36% of participants developed CI or exhibited a clinically significant decline in the 3MS, a more reliable measure of global ability, over 2 years.[15] Moreover, this study also found following adjustment for confounding variables (anaemia, vascular disease, depression etc.) that a significant association remained between eGFR value and CI. Additionally, those with a GFR of <45ml/min per 1.73m^2 were more likely to have reduced global ability.

The majority of the longitudinal studies only used one measure of global ability. Although all but one study confirmed the link between CI and CKD independently of vascular confounders, batteries were not comprehensive enough to describe the pattern of CI. Consequently, two community studies employed an extensive battery assessing multiple domains.[86, 107] Buchman et al[107] found that eGFR was not associated with baseline CI, but was related to the rate of change in episodic (word list recall, delay and recognition), semantic (Boston naming list, verbal fluency) and working memory (digit span), rather than the executive function of processing speed (Stroop task). This relationship persisted after

excluding participants with an eGFR < 30ml/min per 1.73m^2, which also suggests that CI is prevalent in earlier CKD stages rather than exclusively being associated with ESRD. Davey et al[86] yielded similar results, finding that verbal memory and executive functioning declined proportionately with eGFR[86] As previously mentioned, a majority of the longitudinal studies did not include comprehensive batteries. [105, 106, 108-111, 113] However, the included cross-sectional and community studies had larger batteries and provided more information about particular trends of cognitive dysfunction in CKD and HD.

Cross-sectional studies

The most commonly reported finding in both HD and CKD cross-sectional studies was the impairment of performance in the TMT-B, which chiefly assesses inhibitory control, scanning and tracking, and 'psychomotor speed', as listed in table 3. Of eight cross-sectional studies utilising this measure, seven found that a significant number of participants had executive dysfunction according to the Mayo Clinic criteria or the standardised cut-off of >300 seconds.[2, 38, 39, 81, 87, 94, 99] The study that did not find clinically significant impairment in the TMT-B reported that CKD participants took significantly longer to complete the task compared to controls. However, in this study there was evidence for impairment in other facets of WM and EF; 51% of CKD participants compared to 2.5% of controls experienced CI in verbal fluency and delayed recall skills.[95] Additionally, the mean age of participants in this study was relatively young (39 years), suggesting that the extent of CI in this study population may be mild compared to the CKD population at large where a more profound effect on higher functions was observed.

Findings suggestive of poor inhibitory skills and reduced WMC were most frequently documented in studies assessing HD participants (four studies comparing HD and controls, two comparing HD and CKD groups to controls).[2, 38, 87, 90, 99, 101] For example, Murray et al.[38] found that 35-41% of 383 HD participants had 'severe' impairment in four measures of

executive function and memory (visuospatial memory task, digit span, colour trails 1 and 2, clock drawing test) according to the Mayo clinic criteria, compared to 0% in sex, age and education matched controls.[13, 38] A smaller study yielded similar results, finding that measures of executive function (TMT-B, stroop task, verbal fluency, digit span) and memory recall (word list recall, California verbal learning task, digit span) were significantly impaired compared to performance in measures of language and visuospatial abilities.[90] Only one HD study did not report clinically significant findings in measures assessing memory (California verbal learning task) among 50 HD participants.[88] However, performance in measures assessing inhibition, verbal fluency, planning and set shifting (Stroop, backwards digit span, TMT-B) were consistent with other HD studies.[88]

Similar to haemodialysis cross-sectional studies, studies assessing only CKD exhibited impairments in inhibitory control, visual scanning, and re-organizing uncomplicated information (results from Stroop, TMT-B, digit substitution task and digit span), in addition to global cognitive impairment.[80, 93-95, 98] However, there was conflicting evidence as to whether or not these abilities proportionately declined with CKD stage in populations that were recruited from CKD populations as opposed to community-dwelling populations. Although three of these cross-sectional studies have yielded results indicating that a decline in renal function causes a decline in global ability, executive functioning and working memory abilities, this is not enough evidence to firmly support this relationship in this type of study.[80, 85, 94] As such, one study recruiting from a pre-dialytic population found that cognitive status was worse in ESRD participants not receiving dialysis than participants in earlier stages of CKD.[100] However, there was no difference in cognitive function between participants in stage 3 and stage 4.[100] As previously mentioned, this relationship was more frequently documented in cross-sectional and longitudinal community studies.

Overall, the community-based studies had the largest sample sizes (the largest recruited 23,405 participants), and a higher mean age of participant compared to some cross-sectional studies which had younger study populations. However, it should be noted that five of these

studies used a single measure of global cognition, meaning that pattern of CI over time could not be commented upon.[15, 82, 106, 108, 109] Furthermore, three of these five studies used insensitive measures of global cognition (MMSE and 6-CIT).[82, 108, 109] One of these studies performed the test via telephone interview, reducing the reliability of the results.[82] However, ten community studies that used larger batteries or a longitudinal design supported the conclusion that the prevalence of cognitive impairment increased as renal function declined.[22, 23, 81, 83-86, 107, 110, 129] Seven of these studies gave strong evidence that was consistent with cross-sectional haemodialysis and pre-dialytic evidence; not only was renal function associated with global impairment, but reduced psychomotor speed, inhibitory control (TMT-B, Stroop task, digit symbol substitution) and working memory (digit span, immediate and delayed recall) over time.[22, 23, 81, 83, 84, 86, 104]

1.8.7 Systematic reviews and significant limitations

Two systematic reviews were identified which analysed the largest studies (>150 participants) and studies which had participant aged 65 years and older.[128, 130] These reviews were included to gain a clearer perspective on key findings from existing research. Etgen et al.[128] carried out a sensitivity analyses on ten studies in 2012 (7 cross-sectional and 3 longitudinal studies). It was highlighted in this review that there were some important methodological limitations which may account for some of the conflicting results which have been previously explored.

As aforementioned, one longitudinal study did not find any association with CI and CKD.[105] However, this study recruited only male participants, only 21% of which had CKD, and a high attrition rate. Similarly, other studies populations were gender-specific or community-based, limiting generisability as highlighted by Etgen et al.[15, 81, 82, 88, 99, 128] Additionally, there was variability in the number of confounders that were adjusted for, what neuropsychological measures were used, and definition of CI (as illustrated in previous sections) which may cause

discrepancies in results. For example, six studies did not adjust for depressive affect and a further six did not account for effects of CNS-acting medications.[15, 39, 84, 91, 92, 95, 97-99, 104, 108, 113] A British cross-sectional study has also highlighted the need to account for socioeconomic status, in addition to vascular disease risk factors, which no other study has accounted for.[103]

Despite this, Etgen et al[128] revealed in a sensitivity analysis that the association between CI and CKD occurred irrespective of disease stage. However, this association was shown to be stronger in moderate to severe disease (eGFR <45 ml/min per 1.73m^2), rather than mild to moderate CKD (eGFR 45-60 ml/min per 1.73m^2) in longitudinal studies. This finding lends support to the 'dose-dependent' relationship between CKD stage and severity of CI. Another systematic review by Shen et al[130] in 2016 was in agreement with this relationship following analyses of 22 longitudinal studies. Like Etgen et al[128], this review highlighted that CI occurred in CKD independently of age, but that an increase in age causes 'frailty' which may propagate CI.[130] Both reviews also highlighted that CI was consistently present in CKD populations irrespective of age, gender, or vascular disease status. However, the only aspect which was not discussed was the nature and type of impairment which is considered below.

1.8.8 Conclusion

This review aimed to clarify two issues with regards to using the anti-saccade paradigm as a screening tool for CI in CKD. Firstly, this review attempted to bring clarity to the existence of a 'dose-dependent' relationship between severity of cognitive dysfunction and CKD. This connection was explored as Crawford et al.[3, 4] found that the anti-saccade task could discriminate between mild and moderate cognitive impairment in early and moderate Alzheimer's disease. Evidence that supports there is an 'early' stage of CI according to CKD stage prior to dementia conversion helps to validate the argument that the anti-saccade paradigm could be a useful screening tool for CI in this population, as with Crawford et al's research.[3, 4] Despite there are some conflicting reports for this relationship in the literature,

there is strong evidence from empirical research and systematic reviews that there is an association between stage of CKD and severity of impairment. It should be noted that impairment was consistently reported as more severe in HD populations compared to CKD populations not receiving haemodialysis also.

Secondly, this review aimed to identify what cognitive domains were commonly affected in CKD in order to investigate how useful the anti-saccade would theoretically be in measuring impairment in this population, i.e. does the typical pattern of impairment match the abilities the tool measures. The evaluation of current research highlighted that uncomplicated verbal and visuospatial memory abilities were mostly intact, but actively maintaining verbal/ visuospatial information and then manipulating it in order to achieve a task goal was problematic. However, the TMT-B has been extensively used in both HD and CKD populations, and it was consistently shown through this measure and other measures of executive functioning, that the ability to visually scan, 'track', simultaneously inhibit a pre-potent response and set-shift was consistently impaired. These abilities are relied upon when performing the anti-saccade task, as described in the below section.

1.9 Occulomotor studies in MCI and Alzheimer's disease

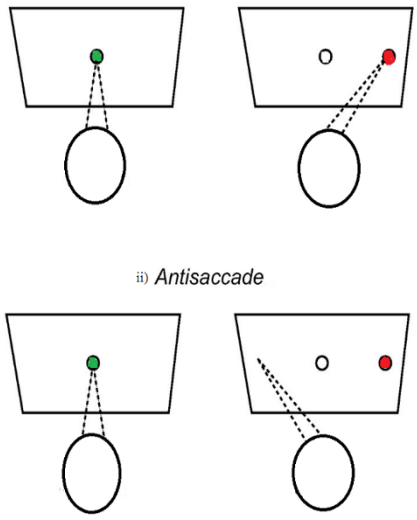
A saccade describes a quick and conjugate movement of the eyes which is usually directed towards a target. When a saccade is purposefully executed in the opposite direction to a specified target, it is referred to as an 'anti-saccade'. The anti-saccade task (AST) was first developed by Hallet[74] in 1978 and has since been used by psychologists, neurologists, and psychiatrists to investigate the underlying neuropathophysiology of a number of health conditions, including those with a CI component.[3, 4, 74, 131, 132] Typically, the AST is accompanied by the pro-saccade task (PST) which assesses visually guided saccades. Visually

guided reflexive saccades, or ‘pro-saccades’, are saccadic eye movements that occur in response to a salient peripheral target. The difference between these paradigms is as follows:

- Pro-saccade task: The eyes are initially presented with a central fixation point. This central visual stimulus disappears and is replaced by a sudden onset peripheral fixation point appears. The participant is instructed to look at both central and peripheral fixation points as quickly as possible as they present themselves individually.

- Anti-saccade task: As with the pro-saccade task, there is an initial transient central fixation point which is followed again by a sudden onset peripheral cue. Participants are instructed to look at the central cue as it appears and to look to the mirror opposite side of the peripheral cue (as accurately and quickly as possible) as it appears.

Figure 6. Schema depicting pro and anti-saccade task



The PST is performed in conjunction with the AST to act as a' reference point' for the analysis of saccadic parameters in the latter more complex task. The following parameters differ in both paradigms:

- Saccade latency: the time taken in milliseconds (ms) from the appearance of a stimulus to the initiation of a saccade in response to the stimulus.[133]

- Saccade duration: The time taken to execute the entire saccade.(ms)[133]

- Saccade peak velocity: The highest velocity reached during the saccade.[133]

- Saccade amplitude: describes the size of the saccade (measured in degrees) this also determines saccade accuracy.[133]

Hallett[74] found in his initial experiment that healthy adults perform the pro-saccade task automatically, quickly and accurately.[74] Comparatively, latencies of correctly performed anti-saccades were slower than those exhibited in the PST.[74] Additionally, it was found that the AST was more challenging to successfully perform compared to the PST, as participants' exhibited an error rate (looking directly at peripheral target) of 5-15% in AST trials compared to 0% in PST trials. [74]These early findings highlight that the AST requires more cognitive effort than the PST, as top-down processes predominately mediate the suppression of reflexive, or 'volitional', saccades in response to salient stimuli and enable 'correct', purposeful eye movement to the opposite hemi-field.[131] However, it has been found since

Hallett's[74] initial experiment that 'healthy' participant's make 'inhibition' errors in the AST (the eyes are instinctively drawn to the target despite the explicit instructions to look to the opposite hemifield) in addition to experimental groups.[4, 134, 135] Usually, these errors are corrected by a rapid eye movement in the intended (opposite lateral) direction.[135] This behavioural corrective response is demonstrative of an individual's innate self-regulatory abilities. Researchers have proposed that EF (goal achievement) and inhibitory control (namely of pre-potent responses and resisting pro-active interference) is central to performing the AST successfully.[66, 75, 131, 134, 136]As discussed in previous sections, EF comprises 'higher order' processes such as planning and attentional control. WM is linked to these sub-processes also, e.g. executive attention. Roberts[75], Kane[69] and Pennington[70] propose that poor overall inhibitory control and a reduced WMC cause goal neglect, and therefore a poor AST performance ; higher error rate, due to inability to resist a captivating stimulus/overcome proactive interference in preference to achieving a task.[69, 70, 75]

As previously discussed in the analysis of CI in CKD literature, this combination of 'higher' abilities are commonly seen to be impaired, particularly in the context of visuospatial inhibitory control (TMT-B). Other groups with CI stemming from a common source to those in CKD populations (inhibitory control, reduced WMC, etc) have exhibited difficulty in performing the AST successfully, namely in pre-AD populations.[3, 4, 132] Crawford et al's[3, 4] research group found in two studies that the ability to self-correct was impaired in early AD populations despite participants understanding task instructions.[3, 4] Moreover, one study in particular highlighted that AD participants made showed that when compared to age matched controls, AD participants produced tenfold more uncorrected errors (25.4% vs 2.5%).[4] In `

both studies, there were correlations between uncorrected anti-saccade errors and measures of EF, working memory and global cognition. Notably, the largest correlations were between TMT-A (r = 0.83) and reverse spatial span (r = 0.83) which primarily measure processing speed, visuospatial memory and planning abilities.[3, 4] In addition to resembling the pattern of impairment consistently shown by CKD populations, it was also found that

uncorrected error rate in the AST was proportional to the severity of dementia in AD participants for two separate measures; the MMSE and Alzheimer's disease assessment scale (ADAS-cog).[3] The ADAS-cog is a more sensitive measure of global ability compared to the MMSE, and the correspondence between AST inhibition errors and ADAS-cog scores supports the argument for the use of AST as a screening tool in the CKD population.

1.10 Oculomotor Studies in CKD

At present, there are no NICE[11] guidelines for diagnosing or managing CI in CKD.[11] In accordance with Wilson and Jugner's screening criteria[137], oculomotor testing may prove to be a preferable screening tool, the benefits of which are manifold.[137] Firstly, as evidenced in the literature review people with CKD that have CI typically show poor inhibitory control and executive dysfunction. These constructs are measured by the AST, making it worthwhile to investigate if the AST is a sensitive tool that could be used to detect CI in this population. Furthermore, Crawford et al[4] have also indicated that uncorrected error rate in the AST correlates with severity of CI in early Alzheimer's disease populations, meaning the AST could potentially identify earlier and more subtle impairment in CKD.

There are also logistical benefits in utilising the AST as a monitoring tool. The experience of attending a memory clinic and completing questionnaires is often daunting for participants who feel under pressure to 'perform'. What is more people with CKD, especially ESRD already attend hospital appointments frequently due to the nature of their treatment. The AST is 'user friendly', and a time efficient method compared to traditional neuropsychological testing, which can be easily used in community dwellings. Additionally, the AST paradigm is not limited by language or literacy skills making it a more acceptable tool to a range of people with differing abilities, unlike other paper-based measures of cognitive functioning. Likewise, unlike paper based neuropsychological tests, eye tracking equipment allows the precise control of sensory input parameters so motor output can be more reliably measured. [55]

Finally, it is not a lengthy process to train health professionals to use oculomotor tests. This could help to reduce the depletion of resources and time within the NHS. An efficient and simple measure to detect CI is certainly needed imminently, as between 2009 and 2010, £1.45 billion was spent in the UK on CKD treatment and its associated healthcare costs.[11] Half of this expense was for ERSD patients, the treatment cost for which doubles each year.[11] As the aging population grows, so does the risk for developing CKD and subsequently dementia. With no clear guidelines on how to proceed with this public health issue, a cross-sectional study examining the relationship between CKD and CI severity with potential to identify a diagnostic tool and subsequent treatment is essential.

2. Hypothesis and Aims

The overall aim of this cross-sectional study is to examine the relationship between the progressive stages of CKD, identify the elements of cognitive function that are impaired and investigate performance of the anti-saccade task in relation to these. Specifically, this study will compare the cognitive function of early stage CKD patients with those receiving dialysis and control participants without CKD. In line with Crawford et al's[4] previous research, the directional hypotheses that will be tested in this study are as follows:

1. The uncorrected error rate in the anti-saccade task will increase as severity of CKD increases; lowest in the control group, higher in the CKD group, highest in the HD group.

2. Cognitive function according to neuropsychological measures will decrease as severity of CKD increases; highest in the control group, lower in the CKD group, highest in the HD group.
3. Uncorrected error rate will increase and neuropsychological performance will decline as eGFR value decreases.

3. Methods and Materials

This section outlines how we recruited participants to test the hypotheses described in the previous section and the techniques used to do so.

3.1 Participants

In order to explore the above hypotheses, a CKD participant group, a HD participant group and a control group needed to be recruited for the study. Initially, 24 CKD patients who met the inclusion criteria had agreed to participate in the study. However, two of these participants subsequently withdrew consent during testing due to feelings of fatigue. Additionally, 29 HD patients were initially recruited, but seven of the participants withdrew consent prior to testing as they felt acutely unwell. Subsequently, a total of 69 participants completed testing; 22 CKD participants, 22 HD and 25 control participants.

All participants in this study were Caucasian. The mean age of the cohort was relatively young also (M = 59.1 years), with an age range of 26-86 years across all participants. Additionally, all of the participants had remained in full-time education until they were at least 16 years of age. Smoking and alcohol consumption was low in the control and experimental groups; none of the participants exceeded an intake of 14 units and the majority of participants were 'never-smokers' (86%). The few participants that were 'ex-smokers' had given up smoking twenty years ago, or longer, previous to testing. This information is detailed in Table 4, page 60.

CKD participants were recruited from outpatient renal clinic in the north west of England, and HD participants were recruited from haemodialysis centres in the same region. Patients were eligible for the study if they were aged 18 years or older, and had between stage one to stage five chronic kidney disease and were not receiving dialysis, or aged 18 years or older and

receiving haemodialysis. However, any patients who had previously received a renal transplant, been diagnosed with/ being investigated for a dementia syndrome, had previously suffered with a Stroke causing neurological deficit, had a psychiatric illness, were currently taking centrally acting drugs, e.g. anti-psychotics or opioid analgesics, were visually impaired or were non-fluent in English language were not eligible for the study. The control group consisted of age-matched volunteers who were partners/spouses of the CKD study group. A proportion of the control participants consisted of volunteers from the Continued Learners group from Lancaster University.

A description of how the total number of participants was calculated in order to reduce the risk of making a type II error in the main hypothesis is shown below.

3.1.1 Power Calculation

A priori power calculation using GPower 3.1 was performed to determine how many participants were required to reduce the likelihood of a type II error occurring when carrying out the main hypothesis. It was found that the minimum number of participants required for the study to have statistical power of 0.8 was 66; 22 HD participants, 22 non- HD CKD participants and 22 control participants. This calculation was made on that assumption of a large effect size ($f = 0.4$) and $\alpha = 0.05$.

3.2 Design

The research design of this study was prospective, cross-sectional and utilised a between-subjects design with three groups; a haemodialysis group, a non-haemodialysis CKD group

and a control group. Testing was carried out on only one occasion using the materials which are described below.

3.3 Materials

3.3.1 Oculomotor testing: eye-tracking equipment

Horizontal saccadic eye movements for both tasks were recorded using a 'Saccadometer advanced' infra-red photo-occulography system, (Ober-Consulting, Poland) with a temporal resolution of 1ms. The central fixation stimulus for both tasks was green and the peripheral stimuli were red. The probability of the peripheral target appearing either left or right of the central fixation point was manipulated to be 0.5. This reduced the likelihood of participants 'predicting' where the peripheral stimuli would appear in both paradigms. The stimuli were projected by head mounted miniature lasers on to a white screen between 1-3m from the participant. Both tasks (anti- and pro-saccade) consisted of 30 trials each. Each task was preceded by 20 pro-saccade calibration trials. This also acted as a set of practice trials for the pro-saccade task. To match this, 5 anti-saccade practice trials preceded the AST. All trials were ordered for all participants as follows: 20 calibration pro-saccade trials, 30 pro-saccade trials, 20 calibration pro-saccade trials, 5 anti-saccade practice trials and 30 anti-saccade trials.

3.3.2 Pro-saccade paradigm

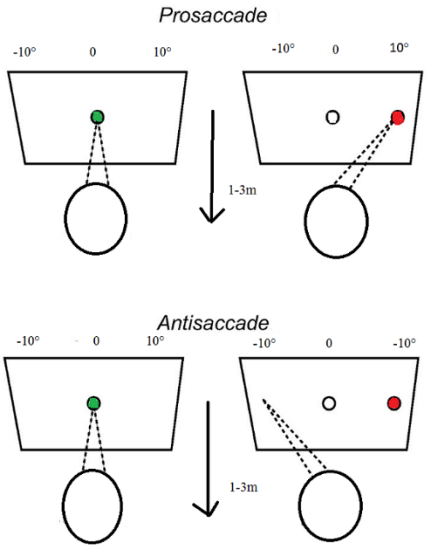
In the pro-saccade task, a green target appeared centrally onscreen, disappeared, and was followed by a red fixation target 10° horizontally right or left of the initial cue. Participants were instructed to look as quickly and accurately as possible at all targets. The central target was present on screen for 1500ms, after a 'gap' of 1000ms the peripheral target would appear onscreen for 2000ms. A new trial would begin (re-appearance of central fixation point),

1500ms after the disappearance of the peripheral target. All trials with a latency of 80ms or less were excluded as this is suggestive of an 'anticipatory' saccade.

3.3.3 Anti-saccade paradigm

As with the pro-saccade task, the green central fixation point appeared centrally, disappeared, and was subsequently replaced by a red target 10° to the right or left of where the central target appeared. Participants were instructed to 'look to the mirror-opposite side of the red target as accurately and as quickly as possible', once the red target appeared in their peripheral vision. To ensure participants understood this instruction, they were asked to verbally explain what was required of them in the AST prior to its initiation. There were also 5 anti-saccade practice trials to ensure participants' understanding of instructions prior to the task. The parameters for the durations of time each target appeared onscreen were identical to those of the pro-saccade task.

Figure 7 Schema illustrating that participants sat 3m from surface that central and peripheral targets were projected on.



3.3.4 Neuropsychological battery

Following the saccade tasks all participants completed a neuropsychological battery. This battery consisted of the Addenbrooke's cognitive examination (ACE-R) final revised version 2005[138], the National Adult Reading Test [139](NART), the digit span (forward and reverse) and spatial span (forward and reverse)[123],and a Stroop task.[140] The Hospital Anxiety and Depression Scale[141] was also administered as a means to detect subclinical anxiety or depression among participants. All tests were administrated in the same order for each participant. A brief description of what each task involved is shown below:

Addenbrooke's Cognitive Examination (ACE-R)

The ACE-R incorporates the MMSE which is scored out of 30, alongside sub-scores for verbal fluency, language, attention, visuospatial abilities and short term memory recall. The combined totals of these components is 100. A higher score indicates better overall global cognitive performance. Similarly, higher scores in individual components indicate better performance in their named constituent. No previous CKD studies have utilised this measure before. However, the ACE-R is a widely used measure that has been validated for use in the community, secondary care settings and 'high prevalence' settings (memory clinics), unlike some of the measures that have been previously used in CKD populations.[121, 138] A score of 88 points of 100 has a sensitivity of 0.84 and a specificity of 0.89 for a diagnosis of MCI in the general population.[121, 138] Therefore, it determined that any participants scoring 88 points or lower in the Addenbrooke's cognitive exam were likely to have global impairment.

NART

The NART is commonly used as a measure of pre-morbid intelligence which is comprised of a list of 50 uncommon words. Participants were instructed to read the list of words aloud; words which were pronounced incorrectly were awarded one point, the total number of incorrectly pronounced words were counted and participants were given a total score ranging between 0 to 50. This score was then used to calculate IQ based on this equation:

$$IQ = 128 - (0.83x \text{ NART error score})$$

The bandings for IQ scores according to the Wechsler Adult Intelligence Scale[123] are as follows: an 'average' IQ score is between 90-109, a 'high average' IQ score is between 110-119, a 'superior' IQ score is between 120-129 and a 'very superior' IQ score is 130 points or above. The NART has been previously used within CKD populations as a measure of pre-morbid intelligence. Additionally, there is strong evidence that the NART has good construct validity of pre-morbid IQ (as opposed to current IQ) in elderly and chronic disease populations that experience cognitive impairment.[39, 142-144]

Digit span

The digit span task required participants to verbally repeat a series of digits which got progressively longer in forward and reverse sequence. The forward digit span is a measure of verbal 'linear' working memory processes, whereas the reverse task requires more 'complex' working memory processes. The forward task contained eight items with two trials comprised of the same number of digits the participant was required to repeat. For example, item one contains two digits in both trials, item two contains three digits in each trial and so on up to nine digits. If both trials are unsuccessfully carried out in one item, the examiner ends the test. The same principle is applied in the reverse digit span task, however there are seven items

rather than eight. Each successful trial is given one point and participants can score between 0-16 in the forward task and between 0 to 14 in the reverse task. A higher score indicates better performance. There are cut-off scores to grade performance in the digit span according to Wechsler's Adult Intelligence Scale.[123] These cut-offs are as follows: In the forward digit span, a score of ten points or more is considered 'above average', a score between six and nine points is considered 'average', and a score of five points of less is considered 'poor'. In the reverse digit span a score of nine points of more is considered 'above average', a score between six to eight points is considered average and a score of five points or less is considered poor.

This measure has been previously used in CKD populations and in MCI populations that have utilised the anti-saccade paradigm.[4, 90, 101] The forward digit span has been found to be a reliable measure of short term verbal memory (phonological loop) with good construct validity, and the reverse digit span has been found to have good construct validity for the measurement of attentional control in the general population and in chronic disease populations.[126, 145]

Spatial span

The spatial span task is highly similar to the digit span task, but participants are required to replicate a 'tapping' sequence performed by the examiner on a black wooden board of blocks (corsi blocks). As with the digit span, the sequences become progressively longer and the task ends if two trials of the same item are performed incorrectly. Both forward and reverse tasks have eight trials each (two blocks in item one increasing to nine blocks in item eight). One point is awarded for each successful trial and scores range from 0 to16 for both tasks. A higher score indicates better performance. A score of less than six points is in the forward spatial span is considered 'poor', whereas a score between seven and eight is an 'average' score, and scores above nine points is 'above average'. Similarly, a score of five points or less

in considered ‘poor’ in the reverse span, a score of between six to eight is ‘average’ and a score of nine or above is ‘above average’. These scores are in accordance with the Wechsler Adult Intelligence Scales.[123]The forward span is a measure of visuospatial short term memory, whereas the reverse span is a measure of complex spatial working memory/ executive functioning.[126]

As with the digit span, the spatial span has been used previously in CKD populations and in MCI populations that also utilised the anti-saccade paradigm. The forward spatial span is a reliable measure of short term spatial memory and attention, whereas the reverse spatial span reliably measures complex spatial attention (holding information and manipulating this in a goal oriented way) and executive functioning.[126]

Stroop task

For the Stroop task, participants were given a sheet of paper displaying 100 words naming five colours printed in a colour of ink not denoted by its name. Participants were instructed to read the colours of ink aloud rather than the name of the word. The time taken, errors made and corrected errors were recorded for each participant. The time taken to perform the Stroop task was used as a measure of executive function; psychomotor speed, the errors made in the Stroop task was used as a measure of inhibitory control, and the corrected errors were used as a measure of self-monitoring. A number of different versions of the Stroop task have been used previously in CKD populations.[38, 80, 88, 90, 99, 101, 104] This lack of consistency therefore made it difficult to decide which measure of the Stroop task to utilise. As such, it was subsequently decided to use a measure which was comprised of 100 words in order to gain a clear and more reliable perspective as to which groups had a slower psychomotor speed, poorer verbal inhibitory control and self-regulation.[140] Ishihara’s 38 plate colour blindness test was carried out before the Stroop task to avoid confounding due to colour-blindness.[146]

The Hospital Anxiety and Depression Score

The HADS is a self-reported 14 item scale that assesses depressive and anxious affect, with seven items corresponding to depressive affect and seven items corresponding to anxious affect. This particular scale was beneficial for the study as it avoids focus on the physical and somatic symptoms of depression and anxiety, e.g. headaches, fatigue, as these may also be present in chronic physical diseases. Each item is scored between 0 to three and the total score of all depressive or anxious symptoms can range between 0 to 21. Scores are categorised into 'no depressive/anxious affect' (0-seven points), mild (eight to ten), 'moderate' (11-14) and 'severe' (>14). The HADS is one of the most widely used measures of affect and has been previously used in the CKD population before.[90, 100] It has good internal reliability and has been shown to be a valid construct of sub-syndromal anxiety and depression. [147, 148]

3.4 Procedure

This section reports what the recruitment process entailed for potential experimental groups' participants, what the testing involved and what information was obtained during the testing process for the database that was subsequently used for statistical analysis.

3.4.1 Patient recruitment process

Potential CKD (not receiving haemodialysis) participants were identified from clinic lists up to three months prior to their appointment. The participant information sheets were posted to eligible individuals at least four weeks prior to their clinic appointment. This information sheet is shown in Appendix 3. Two weeks before the clinic, potential participants were contacted via telephone to establish interest in participation of the study. Understanding of what the study entailed was assessed over the telephone and any questions about what the testing involved were answered. Individuals were also informed that if they subsequently decided against participation on the day of their appointment this would not affect their healthcare. Outpatient testing was carried out before or after individuals' appointments in the

outpatient department. Testing began only after questions regarding the study were answered, it was ascertained they had a good understanding of what the study involved and voluntary and informed consent was obtained. The consent form signifying that participants' agreed to participate in the study is shown in Appendix 4. The order the tests were administered was as follows: Pro-saccade paradigm, anti-saccade paradigm, ACE-R, NART, digit span, spatial span, Stroop task, and HADS. This ordering of test administration was the same for control participants also.

Participants receiving dialysis were approached during their dialysis session and given the participant information sheet (Appendix 3) to consider. A two-week period was then allowed so people could carefully consider their potential participation in the study. Individuals given information sheets were asked via telephone or in person if they wanted to participate. All potential participants were assured that deciding not to participate would not affect their clinical care. Those who voluntarily gave informed consent were tested once it was established that they had a good understanding of what the study involved. There is conflicting evidence in the existing literature concerning the impact timing of dialysis sessions has upon optimal cognitive performance.[91, 149, 150] However, there is no consensus between authors as to when cognitive performance is at its worst so testing was carried out during and after dialysis sessions. Both dialysis units were quiet so there was no interruption to the neuropsychological battery. The oculomotor tasks were carried out in a separate room within the dialysis unit after participants' haemodialysis sessions.

Initially, recruitment of haemodialysis patients occurred from one dialysis centre. However, due to low participation rate a second site was added. This was reflective of the nature of ESRD requiring HD; most people in this subgroup had numerous co-morbidities meaning they did not want to participate. Additionally, a majority of patients receiving in-centre HD met one or more conditions of the exclusion criteria (see Participants section). For example, many had visual disabilities due to comorbid diabetic retinopathy, others had a mental illness

which was being treated with pharmacotherapy, or chronic pain associated with uraemia that required opioid analgesics.

3.4.2 Control recruitment process

Information sheets outlining what the study entailed and why it was being carried out were circulated within the Continued Learners group from Lancaster University, and among potential CKD participants' partners/spouses. This information provided contact details of the authors, so potential participants were given the opportunity to ask questions regarding the study via telephone or e-mail/ arrange a suitable time to participate. Testing was then carried out at the Lancaster University Psychology department, or the outpatient department of the aforementioned hospitals once it was ascertained that participants had a good understanding of what was involved in the study and subsequent voluntary and informed consent was given. Participants were also advised that they could withdraw consent at any stage during testing. Those who travelled to participate were offered £10 towards travel costs so no participant would incur financial loss.

3.4.3 Database

The following results were recorded and compiled to make a comprehensive database for statistical analyses after testing. In addition to demographic information and test results, the blood test results of CKD participants were recorded. The GFR reading for participants with stage 1 and 2 CKD was given as 'GFR >60 ml/min per 1.73m^2, in one NHS trust, causing less accurate readings. However, the second trust used for recruitment gave the precise eGFR readings for those in early CKD stages. For all participants with later stages of CKD a precise GFR reading was given. The eGFR of CKD and HD participants was obtained within two weeks of cognitive testing. This timeframe is smaller than what is observed within existing

literature; previous studies mostly obtained blood results that were recorded from samples taken one or two months prior to cognitive testing.[15, 79, 94]

Information obtained from all participants:

- Demographic Information:
    - Age
    - Gender
    - Years of Education
    - Smoking status
    - Weekly alcohol intake

- Medical Information:
    - Comorbidities
    - Medication use

- Oculomotor task parameters:
    - Percentage of anti-saccade errors
    - Percentage of corrected anti-saccade errors

- Neuropsychological battery:
    - ACE-R score (maximum score of 100)
    - NART (maximum score of 50)

- Time in seconds taken to complete the Stroop task
- Number of errors in Stroop task
- Number of corrected errors in Stroop task
- Individual item score of 14 items in HADS (0-3)
- Forward and reverse digit span scores (maximum score of 16 or 14, respectively)
- Forward and reverse spatial span scores (maximum score of 16 for each)

Obtained only from CKD participants:

- Aetiological cause of CKD
- Dialysis status
- Blood results:
    - Estimated GFR (eGFR)

Obtained only from haemodialysis patients:

- Number of months receiving haemodialysis

3.5 Statistical Analysis

Data were analysed using SPSS for Windows version 22.0. There were no missing data values in the study. Kolmogorov–Smirnov's test was carried out to investigate the normality of demographic, anti-saccadic and neuropsychological data. As none of these data deviated from the normal distribution, they were not reported on or subsequently transformed. For all continuous descriptive data means and standard deviations were calculated. This included some of the demographic variables (age, years of education, weekly alcohol intake),

neuropsychological battery scores and uncorrected error rate in the anti-saccade task. Percentages were calculated for categorical descriptive data, e.g. smoking status and gender. One way ANOVAs were calculated to make comparisons of the anti-saccade task data and scores in the neuropsychological battery across the control and experimental groups for the first and second directional hypotheses. The same process was carried out for the demographic covariates to investigate if these variables significantly differed ($p < 0.5$) between the three groups. This was performed to investigate if any demographic covariates potentially exerted a confounding effect upon cognitive status. Levene's test was carried out alongside all one-way ANOVAs to investigate if any data violated the assumption of homogeneity of variances. Any of these data that violated Levene's test for homogeneity of variances were submitted to Welch's ANOVA as a post-hoc test to verify significance.[151] Comparisons where overall ANOVA/ Welch's ANOVA was significant at the $p < .05$ level were further verified using Games-Howell's test post-hoc. This allowed for more specific comparisons to be made across the three groups where a significant interaction was found. For the third hypothesis, Pearson's correlations were performed with two-tailed significance between the anti-saccade task uncorrected error rate and demographic covariates, and between all of the neuropsychological measures and demographic covariates for all CKD participants. Demographic covariates that had significant correlations at the $p < 0.05$ level for the anti-saccade task or any of the neuropsychological measures were entered into a multiple regression as 'predictor variables' alongside eGFR (primary measure of CKD), and uncorrected error rate in the anti-saccade in the regression models that attempted to analyse each neuropsychological measure. Consequently, ten multiple regressions were reported. It should be noted that the significance level $p < 0.05$ was applied to all results of the investigated hypotheses to reduce the chance of making a type I error.

3.6 Ethical Approval

The study was given a favourable opinion from the East Midlands Nottingham research ethics committee, with reference: 14/EM/1195. Thereafter, all ethical procedures were followed for recruitment of participants within the NHS.

4. Results

This section summarises all of the participants' demographic information, in addition to oculomotor task and neuropsychological performance. A sub-section describing the inferential statistics that were carried out for each hypothesis is also included.

4.1 Descriptive Statistics

This section details the demographic information (age, gender and education information) and lifestyle data (smoking status and weekly alcohol intake) in addition to information regarding participant mood (Hospital Anxiety and Depression scale) and CKD information (aetiology of CKD, disease severity).

4.1.1 Demographic and lifestyle factors

A summary of all 69 participants' characteristics and Hospital Anxiety and Depressions Scale scores are shown in table 4 (see page 60). Following a series of one-way ANOVAs all variables as shown below as $F > .18$, $df > 2,66$, and $p > .06$, in table 4 were considered to be non-significant.

4.1.2 Other descriptive data

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale consists of two subjective sub-scales; seven items measure psychological symptoms of anxiety and seven items measure psychological symptoms suggestive of depressive affect. The mean score for both subscales across all three participant groups was relatively low. According to the cut-off scores for both scales, the majority of participants exhibited no symptoms suggestive of subclinical, non-somatic symptoms of depression or anxiety. Further information regarding the clinical 'bandings' for each group are shown in table 4 (page 60). As with the demographic and lifestyle information, both of the HADS scores were statistically non-significant between the three groups following one-way ANOVA analyses.

As is usual when employing tests in a population that measure different constructs with multiple item responses, the correlation of observed scores with 'true' scores should be quantified. Therefore, Cronbach alphas were calculated as an indicator of internal reliability. Both scales displayed moderate, but acceptable levels of internal consistency in the participant population as determined by Cronbach's alpha of 0.76 in the anxiety subscale, and 0.70 in the depression subscale.

Table 4 Demographic and HADS data for all participants

Characteristics	Participants (*N* = 69)	Controls (*n* = 25)	CKD (*n* = 22)	HD (*n* = 22)	*F*	*df*	*P*	Cronbach's α
Age, mean years *(SD)*	59.1 (16.4)	54.8 (14.7)	61.8 (17.8)	61.1 (16.9)	1.34	2,66	0.3	
Female, *n (%)*	34 (49)	15 (60)	11 (50)	8 (36)	0.47	2,66	0.6	
Education mean years *(SD)*	15.1 (2.9)	16.2 (3.1)	14.5 (2.2)	14.6 (3.0)	2.59	2,66	0.08	
Mean weekly alcohol unit intake *(SD)*	2.8 (4.3)	5.2 (5.4)	2.3 (3.5)	0.7 (1.4)	7.97	2,66	0.06	
Smokers, *n (%)*	5 (7)	2 (8)	2 (9)	1 (5)	0.18	2,66	0.8	
Ex-smokers, *n (%)*	5 (7)	2 (8)	1 (5)	2 (9)	0.30	2,66	0.7	
Never-smokers, *n (%)*	59 (86)	21 (84)	19 (86)	19 (86)	0.34	2,66	0.9	
HADS Anxiety mean score *(SD)*	5.4 (2.8)	5.1 (2.8)	4.9 (3.0)	5.1 (2.8)	0.32	2,66	0.7	0.76
HADS Anxiety score 'normal' , *n (%)*	58 (84)	22 (88)	20 (91)	16 (73)				
HADS Anxiety score 'mild', *n (%)*	8 (12)	1 (2)	1 (5)	6 (27)				
HADS Anxiety score 'moderate', *n(%)*	3 (4)	2 (4)	1 (5)	0				
HADS Depression mean score *(SD)*	3.5 (2.7)	2.4 (2.4)	5.1 (3.0)	2.4 (2.4)	5.43	2,66	0.2	0.70
HADS Depression 'normal' score , *n (%)*	62 (90)	24 (96)	21 (95)	17 (77)				
HADS Depression 'mild' score , *n (%)*	5 (7)	0	1 (5)	4 (18)				
HADS Depression 'moderate' score , *n (%)*	2 (3)	1 (4)	0	1 (5)				

Note. *p* value relates to oneway between-subject ANOVA

4.1.3 Aetiology of CKD

The aetiological cause of CKD was recorded for each participant (*n* = 44) and is shown in table 5 (page 62). The most common causes were glomerulonephritis (*n* = 17; 39%) and renovascular disease, which included diabetic/hypertensive nephropathy and atherosclerosis of renal arteries (*n* = 11; 25%). For the other participants, CKD was resultant of hereditary disease (polycystic kidney disease), extensive renal scaring (focal segmental glomerulosclerosis) or an unknown aetiology. Of the remaining eight aetiologies listed as 'other' in table 5, eight participants had been the given the following diagnoses: Amyloidosis, multiple myeloma, ethyl glycol poisoning, type I renal tubular acidosis, loin pain haematuria syndrome, persistent non-visible haematuria syndrome, IgG nephropathy and utero-pelvic

junction obstruction. Generally, these aetiologies (including glomerulonephritis) are considered ‘rare’ causes of CKD. Vascular disease is the most common cause of CKD in the developed world, yet this was not the case in the study population. This is likely to be because of the ‘young’ age of the population; prevalence of hypertension and atherosclerosis increases with age. Hence, this study’s population had a larger proportion of less people with less commonly occurring aetiologies.

4.1.4 CKD Severity

The participants in the CKD group were categorized according to the different CKD stages according to KDIGO guidelines based on their eGFR readings, as shown in table 5 (page 62). People receiving haemodialysis are considered to be in End Stage Renal Disease (ESRD), regardless of their eGFR value. As such, none of the 22 participants from the HD group’s eGFR values are listed in table 5. A minority of the CKD participants had ‘early stage’ CKD (KDIGO stage 2 CKD or earlier), (n = 5; 22.7%), nearly half had ‘moderate’ CKD (KDIGO stages 3A and 3B), (n = 10; 45.5%), and the remainder had ‘late stage’ CKD (KDIGO stages 4 and 5). All HD participants received three haemodialysis sessions a week, lasting between three and a half to four hours. The mean number of months HD participants had been receiving haemodialysis for was 26 months with range 13-122 months.

Table 5: Summary of aetiologies and eGFR ml/min per 1.73m^2 for CKD and HD groups

Characteristics	All participants (*n* = 44)	CKD (*n* = 22)
Cause of CKD, *n (%)*		
Glomerulonephritis, *n (%)*	17 (39)	
Renovascular disease, *n (%)*	11 (25)	
Unknown aetiology, *n (%)*	4 (9)	
Focal segmental glomerulosclerosis, *n (%)*	2 (5)	
Polycystic kidney disease, n *(%)*	2 (5)	
Other, *n (%)*	8 (18)	
Mean eGFR ml/min per 1.73m^2 *(SD)*	23.6 (21.8)	39.3 (21.3)
Stage 1 and 2, >60ml/min per 1.73 m^2, *n (%)*		5 (23)
Stage 3A 45-59, ml/min per 1.73 m^2, *n (%)*		6 (27)
Stage 3B, 30-44, ml/min per 1.73 m^2, *n (%)*		4 (18)
Stage 4, 15-29, ml/min per 1.73 m^2, *n (%)*		4 (18)
Stage 5, <15 ml/min per 1.73 m^2, *n (%)*		3 (14)

4.1.5 Neuropsychological measure descriptive data

The following section includes a descriptive summary of participants' results in the neuropsychological battery. Table 6 (page 70) details the groups' mean scores for these measures.

ACE-R

The measure used to measure global ability was Addenbrooke's cognitive exam. A score of 88 out of 100 points or less was indicative of global impairment in this measure. In the study population, none of the controls had a score of 88 points or less. Four (18%) out of twenty-two CKD participants scored less than 88 points. Lastly, six of twenty-two (27%) HD participants achieved a score of 88 points or less in the Addenbrooke's cognitive exam.

NART

The National Adult Reading Test (NART) is a measure of pre-morbid IQ. The bandings of the IQ scores were applied to the study population (as shown in the Method section). According to the Wechsler Adult Intelligence Scale bandings, one (4%) control, five (23%) CKD participants and eleven (50%) HD participants had an 'average' IQ. Thirteen controls (52%), fourteen (64%) CKD participants and ten (45%) HD participants had a 'high average' IQ. Lastly, eleven (44%) controls, three (14%) CKD participants and one (5%) HD participant had a 'superior IQ' according to the NART.

Digit span

The digit span was one of the measures of working memory and executive functioning. The forward digit span is scored between zero and 16, and the reverse digit span is scored between zero and 14. Standardized cut-off scores for the forward and reverse digit spans have been published as part of the Wechsler Adult Intelligence Scales[123] which are shown in the Method section. According to these cut-offs, none of the controls, two (9%) CKD participants and none of the HD participants were in the 'poor' category for the forward digit span. One (4%) control, five (23%) CKD participants, and seven (32%) HD participants were in the 'poor' category for the reverse digit span.

Spatial span

The forward and reverse spatial spans are also measures of working memory and executive functioning. Both measures are scored between zero to sixteen. As with the digit span, standardized cut-offs exist for the spatial span as part of the Wechsler Adult Intelligence

Scales[123], which is shown in the Method section of this thesis. According to these values, in this study's population eight (32%) controls, seven (32%) CKD participants and eleven (50%) HD participants achieved a poor score in the forward spatial span. Additionally, seven (28%) controls, seven (32%) CKD participants, and thirteen (59%) HD participants were in the 'poor' category for the reverse spatial span according to the standardized cut-off values.

Stroop task

Lastly, the time taken to complete the Stroop task, the total amount of errors participants made and subsequent Stroop uncorrected error rate were used to measure different components of executive functioning (inhibitory control, set shifting and self-monitoring.) Overall, the CKD participants took longer to complete the task than the controls, indicating that there was an 'accuracy-speed' trade off in the experimental groups.

4.2 Inferential Statistics

This section will report the inferential tests that were carried out (and subsequent results) to analyse the three directional hypotheses made which were as follows:

1. The uncorrected error rate in the anti-saccade task will increase as severity of CKD increases; lowest in the control group, higher in the CKD group, highest in the HD group.

2. Cognitive function according to neuropsychological measures will decrease as severity of CKD increases; highest in the control group, lower in the CKD group, highest in the HD group.

3. Uncorrected error rate will increase and neuropsychological performance will decline as eGFR value decreases.

4.3 Hypothesis 1: Anti-saccade task: the uncorrected error rate in the anti-saccade task will increase as severity of CKD increases

The first and main hypothesis predicted that uncorrected error rate in the anti-saccade task would be largest in the HD group, lower in the CKD group and lowest in the control group. The direction of this hypothesis was made based upon indications given in prior research that CI in CKD may be more severe in later stages of the disease (i.e. ESRD including those receiving haemodialysis). A one-way ANOVA was carried out in order to identify any statistically significant differences between the mean uncorrected error rate in the anti-saccade task. Where the homogeneity of variances was violated, Welch's oneway ANOVA was carried out to confirm statistical significance between variables. Games-Howell's test was also used to identify which means among the three groups were statistically significant. These data are presented in table 6 (page 70).

Initially, it was found that the homogeneity of variances was violated (Levene's test p=0.002). However, when a one-way Welch's ANOVA was carried out as post-hoc testing the difference in means remained statistically significant, Welch's F (2, 39.969) = 4.102, p = 0.02. A Games-Howell test was subsequently performed to further investigate the difference between the group means. The mean increase in uncorrected errors between the control group (M = 4%, $S.D$= 30.6) and CKD group (M = 15%, $S.D$=27.1) was 11.45 [CI -3.85-26.74], which was not statistically significant (p = 0.18). However, the difference in means for the control group and the HD group (M = 24%, $S.D$ = 32.5) for uncorrected errors was 20.67 [CI 1.43-39.91], which was statistically significant (p = 0.03). Lastly, the difference in

uncorrected error means between the CKD and HD group (*M*= 9.2) was not found to be statistically significant [CI -11.73-30.30].

4.4 Hypothesis 2: Cognitive function according to neuropsychological measures will decrease as severity of CKD increases

The second hypothesis predicted that performance in the neuropsychological battery would be lowest in HD participants, higher in the CKD group and highest in the control group. As with the first and main hypothesis, the second hypothesis was given this direction due to previous research indicating that CI in CKD was more prevalent and severe in later stages of CKD. A series of oneway ANOVAs was carried out to assess for statistically significant differences between the means of the neuropsychological measures in the groups. Where homogeneity of variances was violated, Welch's ANOVA was subsequently carried out as a post-hoc test to determine if any statistically significant results remained as such. Additionally, Games-Howell's test was employed to investigate which groups statistically significantly differed from each other. Table 6 (page 70) shows the mean scores and standard deviations of the neuropsychological measures for the control and experimental groups.

Additionally, individual scores in the neuropsychological measures were also analysed according to their standardised cut-off values, as with the HADS, to investigate prevalence of impairment. Where measures did not have established cut-offs for cognitive impairment, mean scores that were published in the literature (CI in CKD) were used as a reference point. The measures used in this study and what they measured were as follows: Addenbrooke's cognitive examination (ACE-R) which measured global ability, the NART (pre-morbid intelligence), forward and reverse digit span (working memory and executive function), forward and reverse spatial span (working memory and executive function), time taken to complete the Stroop task (executive function; psychomotor speed) Stroop total errors

(executive function; inhibitory control) and Stroop uncorrected error rate (executive function; self-monitoring). The next section will explore performance in these individual measures.

4.4.1 Neuropsychological data inferential statistics

As previously stated, a series of oneway ANOVAs was carried out to establish if the differences between mean scores of the neuropsychological measures between the three groups was statistically significant. As shown in table 6 (page 70), the differences between the forward digit span, forward spatial span and uncorrected error rate in the Stroop task were statistically non-significant.

The differences between the means of the NART, time taken to complete the Stroop and total Stroop errors were initially found to be statistically significant, but homogeneity of variance was violated for each of these measures according to Levene's test (NART $p = 0.02$, Stroop time $p = 0.001$, total Stroop errors $p = 0.01$). To establish if the difference in means for these tests were truly statistically significant, post-hoc Welch ANOVAs and Games-Howell tests were carried out. Following these tests, it was found that the difference in means between the three measures remained statistically significant, as shown in table 7 (page 72). The differences between the groups' neuropsychological measures means were assessed using Games-Howell's test for all statistically significant results (listed in table 6 page 70).

ACE-R

In Addenbrooke's cognitive examination, the difference in means between the controls and CKD group was 4.25 [CI 1.01-7.49], which was statistically significant ($p = 0.008$). The difference in means between the control group and the HD group was 5.48 [1.79-9.16], and was also statistically significant ($p = 0.003$). The difference in means for the ACE-R between the CKD and HD groups was 1.23 [CI-2.96-5.12], which was non-significant ($p = 0.8$).

NART

For the NART, the mean difference in IQ between the control group and the CKD group was 4.2 points [CI 0.58-7.8], with a significance level of $p = 0.02$. The mean difference between the control group and the HD group was 7.5 [CI 2.7-12.32], with a significance level of $p < 0.001$. Lastly, the mean difference between the CKD and HD groups was 3.3 points [CI -2.14-10.05], however this was non-significant $p = 0.3$.

Digit span

Games-Howell's test was not used for the forward digit span as the difference between the mean scores for this measure was non-significant between the groups. Although Games-Howell's test was carried out on the reverse digit span, as a significant difference was found between the groups' mean in this measure (table 6, page 70). The mean difference between the control and CKD group was 1.67 [CI -.01-3.36], and was statistically significant ($p = 0.05$). The mean difference between the control group and the HD group was 2.31[CI.49-4.12], which was also statistically significant ($p = 0.01$). However, the mean difference between the CKD and HD groups was 0.64 [CI-1.25-2.52], which was non-significant ($p = 0.12$).

Spatial span

The difference in means in the spatial forward and reverse spatial spans between the control and experimental groups was non-significant, therefore, Games-Howell's test was not used to further examine differences in these mean scores.

Stroop task

Alternatively, as a statistically significant difference was found between mean Stroop times Welch's F (2,40.6) =12.514, $p < 0.001$, Games-Howell's test was performed. It was shown that the mean difference in Stroop task times between the control and CKD group was 27.44 seconds [CI 1.59-53.30], with a statistical significance of $p = 0.04$. The mean difference between the control and HD group was larger at 69.76 seconds [CI 34.71-104.82], with a statistical significance of $p<0.001$. Lastly, the mean difference between the CKD and HD groups was 42.32 seconds [CI 5.29- 79.34], with a statistically non-significant level of $p = 0.2$. There was also a statistically significant difference found between the groups' mean total Stroop errors, Welch's F (2,35.6) = 3.65, $p = 0.04$. Games-Howell's test revealed that the mean difference between the control and HD group in this measure was 3.06 [CI 0.39- 5.73] which was statistically significant at $p = 0.021$. The mean difference between the control and CKD group was 1.15 [CI -1.64- 3.94], which was statistically non-significant ($p = 0.6$), as was the difference in means between the CKD and HD group, 1.90 [CI -5.32- 1.5], $p = 0.4$. The final measure, Stroop uncorrected error rate, did not significantly differ between the groups and was not subsequently analysed using Games-Howell's test.

Table 6. Summary of neuropsychological battery performance for participants

Neuropsychological measure (N = 69)	Controls (n = 25)	CKD (n = 22)	HD (n =22)	Measure range	F	df	p
ACE-R, mean (SD)	96.8 (3.6)	92.6(5.2)	91.4(6.2)	0-100	7.71	2,66	0.01
NART IQ, mean (SD)	118.3 (4.5)	114.1(5.5)	110.7 (8.2)	0-50	8.71*	2,49.8	<0.001
Digit span forward , mean (SD)	11.6 (2.1)	10.5(2.4)	10.8(2.2)	0-16	1.77	2,66	0.2
Digit span reverse ,mean (SD)	9.1 (2.3)	7.4 (2.4)	6.7 (2.7)	0-14	5.45	2,66	0.006
Spatial span forward ,mean (SD)	7.5 (1.8)	7.1 (1.7)	6.6 (1.9)	0-16	1.4	2,66	0.3
Spatial span reverse ,mean (SD)	6.6 (1.6)	5.8 (1.4)	5.6 (1.7)	0-16	2.95	2,66	0.06
Stroop time in seconds ,mean (SD)	101.9(33.0)	129.4(33.0)	171.7(59.3)		14.32*	2,40.6	<0.001
Stroop total errors ,mean (SD)	1.4 (1.7)	2.6 (3.0)	4.5 (1.2)	0-100	3.82*	2,35.6	0.008
Stroop corrected error rate (%) ,mean (SD)	30.6(6.1)	89.7 (19.5)	85.6 (21.7)	0-100	0.61	2,66	0.8

Note. F denotes overall ANOVA; * Welch's F values; p value relates to oneway ANOVA

4.5 Hypothesis 3: Uncorrected error rate will increase and neuropsychological performance will decline as eGFR value decreases.

This section will report the inferential statistics used to analyse the third, and last, hypothesis: as eGFR decreases, the uncorrected error rate in the anti-saccade task will increase and performance in the neuropsychological measures will decrease, i.e. does a 'dose-dependent' relationship exist between CKD stage and cognitive performance. The direction of this hypothesis was determined as such due to indications in previous CI in CKD literature that CI

was more prevalent in later stages of CKD and in HD populations. In order to investigate this hypothesis, a series of regressions were performed to investigate if stage of CKD was predictive of cognitive performance over other potential confounding covariates. Additionally, regressions were also carried out to ascertain whether or not the uncorrected error rate predicted cognitive performance as with Crawford et al[4]'s study.

To achieve this, preliminary Pearson's correlations were carried out at two-tailed significance level, between anti-saccade uncorrected error rate and demographical covariates (age, education, smoking, alcohol intake, HADS anxiety and depression score) in CKD participants. The same process was then carried out for all measures comprising the neuropsychological battery and the demographical covariates in CKD participants as listed above. Any demographic variables that corresponded with the uncorrected error rate, or any neuropsychological measures at the significance level $p < 0.05$ were then subsequently entered in to a multiple regression model with eGFR to investigate which covariate (eGFR or demographic variable) was most likely to predict uncorrected error rate in the AST/ neuropsychological measure performance. The same was then carried out for each of the neuropsychological measures; multiple regression models were used to determine which variable (eGFR, demographic covariates significant at $p<0.05$, or uncorrected error rate) was most predictive of performance in each specific measure. A summary of all the correlations that were performed is shown in table 7, page 72.

Table 7. Pearson's correlation values between cognitive measures and demographic variables

Cognitive Measure	Age	Education	Alcohol Units	Smoking	Anxiety score	Depression score
Uncorrected error rate (%)	-.38*	-.41**	-.17	.05	-.20	.03
ACE-R	-.27	.36*	.34	-.04	-.13	.08
NART	.11	.53**	.13	.08	.05	-.08
Digit span forward	-.23	.27	.16	-.13	.01	.02
Digit span reverse	-.46**	.25	.30	-.11	-.15	-.16
Spatial span forward	-.46**	.40*	.22	-.16	-.15	.07
Spatial span reverse	-.39**	.16	.01	-.12	-.19	-.18
Stroop time (s)	.67**	-.31*	-.33	.14	.07	.22
Stroop total errors	.33*	-.22	-.04	.20	.12	-.09
Stroop uncorrected errors (%)	.33	-.21	-.12	.18	.02	-.24

Note. ***p*<0.05; ****p*<0.001

As shown above in table 7 (page 72), participants' age positively correlated with uncorrected error rate (r = .38, p = 0.03), Stroop time (r = .67, p <0.001), total Stroop errors (r = .33, p = 0.03) and negatively correlated with the forward spatial span (r = -.46, p = 0.002) and reverse spatial span (r = -.39, p = 0.01). This means that as age (in years) increased, CKD participants had a larger uncorrected error rate in the anti-saccade task, took longer to complete the Stroop task, and made more errors in the Stroop task at a statistical significance level of $p < 0.05$. Additionally, these findings also indicate that as age increased, CKD participants had a lower score in the forward and reverse spatial span at a statistical significance level of $p < 0.05$. Overall, these findings suggest that as age increased, cognitive performance in the anti-saccade task, Stroop task, forward and reverse spatial span decreased.

Moreover, years of education positively correlated with Addenbrooke's cognitive exam (r = .36, p = 0.02) and the NART (r = .53, $p < 0.001$), and negatively with the anti-saccade

uncorrected error rate (r = -.41, p = 0.006) and Stroop time (r = -.31, p = 0.04). These findings indicate that as years of education increased among CKD participants, so did scores in Addenbrooke's cognitive exam and the NART at a statistical significance level of p<0.05. Additionally, as years of education increased, uncorrected error rate in the anti-saccade task decreased and time taken to complete the Stroop task decrease at a statistical significance level of p <0.05. In summary, these findings indicate that as years of education increase, cognitive performance in the anti-saccade task, Addenbrooke's cognitive exam, NART and the Stroop task declined. No other variables (smoking, alcohol unit intake, HADS anxiety and depression score) were entered in to subsequent regression models as they did not show any statistically significant associations with anti-saccade uncorrected error rate or any measures comprising the neuropsychological battery.

A series of multiple regressions were then carried out to establish firstly which variable was most predictive of uncorrected error rate in the anti-saccade task. The independent variables entered into this model were eGFR, and any demographic covariates found to be significant at $p < 0.05$ (see table 7). Then, a further nine multiple regressions were carried out to clarify which covariate (of eGFR, anti-saccade uncorrected error rate, and significant demographic covariates) was most predictive of each neuropsychological measure. The results of each regression model are stated below.

4.5.1 Anti-saccade uncorrected error rate

A multiple regression that predicted uncorrected error rate in the anti-saccade task in CKD participants was based upon three variables (eGFR, age and education) and was found to be statistically significant F (3,40)=4.74, p = 0.006 . The model explained 21% of the variance. One significant independent variable emerged; years of education (β = -.36, p = 0.02). The other two variables were non-significant; eGFR and age.

4.5.2 ACE-R

The regression used to predict Addenbrooke's cognitive examination score consisted of three predictor variables (eGFR, uncorrected error rate and years of education), and indicated a significant model $F(3,40)=2.91$, $p = 0.046$ which accounted for 12% of the variance. One of the independent variables appeared to be significant; years of education ($\beta = .40$, $p = 0.015$). Uncorrected error rate was non-significant as was eGFR.

4.5.3 NART

The regression which was used for the NART had three independent variables (years of education, eGFR and uncorrected error rate), and was found to be statistically significant $F(3,40)= 6.03$, $p = 0.02$, which explained 26% of the variance. One of the predictor variables were significant; years of education ($\beta =.54$, $p = 0.01$). The remaining variables were non-significant; eGFR and uncorrected error rate.

4.5.4 Digit span

The regression used to predict forward digit span had two independent variables (eGFR and uncorrected error rate) and was not found to be significant $F(2,41)=0.90$, $p = 0.4$). Therefore, further interpretation (percentage of variance and significance level of independent variables) was not carried out.

However, the regression used to predict reverse digit span score, from eGFR and uncorrected error rate was found to be significant, $F(2,41)=4.01$, $p = 0.01$. The independent variables explained 12% of the variance. Subsequently, uncorrected error rate emerged as a significant predictor ($\beta = -.40$, $p = 0.009$), rather than eGFR.

4.5.5 Spatial span

Three independent variables (eGFR, uncorrected error rate and age) were entered in the regression which was used to predict forward spatial span, which was statistically significant $F(3,40)=5.78$, $p = 0.002$, and explained 26% of the variance. Of these three variables, two were statistically significant; uncorrected error rate ($\beta = -.29$, $p = 0.05$) and age ($\beta = -.36$, $p = 0.02$), while eGFR was not.

Similarly, the regression model used to predict reverse spatial span based upon the variables; eGFR, uncorrected error rate and age were found to be statistically significant $F(3,40)=3.99$, $p = 0.01$, which explained 15% of the variance. Age was found of borderline statistical significance; ($\beta = -.29$, $p = 0.06$). Whereas uncorrected error rate and eGFR were not found to be significant.

4.5.6 Stroop task

The regression model that predicted time taken to complete the Stroop task based upon three independent variables (uncorrected error rate, eGFR, and age) was found to be statistically significant, $F(3,40)=17.21$, $p < 0.001$, and accounted for 53% of the variance. Two of the independent variables were statistically significant; eGFR ($\beta = -.34$, $p = 0.003$) and age ($\beta = .63$, $p < 0.001$). Uncorrected error rate, the remaining independent variable, was non-significant.

The model used to predict total errors in the Stroop task included three independent variables (uncorrected error rate, eGFR, and age), and was found to be statistically significant, $F(3,40)=4.52$, $p = 0.008$, which explained 19% of the variance. Uncorrected error rate was the only predictor variable which was found to be statistically significant ($\beta = .35$, $p = 0.23$), rather than eGFR or age.

Lastly, the regression model used to predict uncorrected error rate in the Stroop task, based upon two predictor variables (eGFR and uncorrected error rate), was not found to be statistically significant, $F(2,41)=2.05$, $p = 0.141$. Therefore, further interpretation of the results was not performed.

5. Discussion

This section will summarize the results which were reported in the previous section, attempt to relate these findings to previous research, and suggest directions for further work. The overall purpose of this study was to investigate the effectiveness of the anti-saccade task in detecting cognitive impairment in chronic kidney disease. Those diagnosed with CKD have a higher risk of developing dementia compared to the general population.[1, 25] This is due to an assortment of factors; a higher vascular disease risk, a greater risk of depressive affect, haemodialysis, and the toxic effect exerted directly by CKD itself.[25] There is consistent evidence that CKD is an independent risk factor for developing cognitive impairment and dementia; multiple studies have shown that CI exists in different CKD populations irrespective of concurrent vascular disease, psychiatric illness, age or educational attainment.[2, 15, 38, 84, 94, 104] Considering this, it would be beneficial to develop a non-expensive screening tool that detects cognitive impairment within this high-risk group, irrespective of literacy or language skills and cultural background. Therefore, this study aimed to trial the anti-saccade task as a screening tool in CKD and haemodialysis populations in a prospective, cross-sectional analyses, as it has previously shown potential efficacy as a screening tool in MCI and Alzheimer's disease. The particular facets of cognition affected in CKD were also investigated in this study by the use of traditional neuropsychological measures, in addition to the anti-saccade task. Lastly, to see how the anti-saccade functioned as a screening tool, we

examined if a ‘dose-dependent’ relationship existed between disease stage, extent of impairment and anti-saccade task performance. The answers to these research questions are presented below, followed by an analysis of the findings.

5.1 Summary of results

The first hypothesis predicted that uncorrected error rate in the anti-saccade task would increase according to disease severity; healthy controls would have the lowest uncorrected error rate, CKD participants would exhibit a higher uncorrected error rate and HD participants would have the highest rate of uncorrected errors. This hypothesis was supported in that HD participants performed significantly worse than control participants in the anti-saccade task. However, there was no difference between the controls’ and CKD group’s performance in the anti-saccade task in terms of uncorrected error rare, or between performance in the experimental groups (CKD and HD). These results were not impacted by participants’ age, level of education, alcohol consumption, smoking status, or feelings of depression or anxiety.

The second hypothesis indicated that performance in the neuropsychological battery would also decline as disease severity progressed. HD participants would exhibit the lowest performance in the neuropsychological battery, CKD participants would score higher and the control participants would score the highest. Again, the data somewhat supported this hypothesis. Controls exhibited higher levels of cognitive functioning compared to the experimental groups, according to scores in the neuropsychological battery. However, there was no observable difference between the CKD and haemodialysis group in terms of cognitive function according to the neuropsychological battery.

For example, the control participants achieved higher scores than the CKD and HD groups in Addenbrooke’s cognitive exam (ACE-R), but the CKD group did not achieve better scores than the HD group. The control group also had significantly higher IQs as reported by the

National Adult Reading Test (NART) than both of the experimental groups. However, there was no significant difference between IQ scores in the experimental groups. Additionally, the controls scored higher in the reverse digit span (working memory) and took less time to complete the Stroop task (measures of executive function; psychomotor speed) than both haemodialysis and pre-dialysis participants. Similarly, the control participants made less total errors in the Stroop task than the haemodialysis participants. However, there was no evidence that the controls made less errors in the Stroop task than the CKD participants.

For the remainder of neuropsychological measures, there was no evidence that any group had a higher performance over another. Therefore, it should be interpreted that passive visuospatial memory (forward spatial span) and visuospatial working memory and executive functioning (reverse spatial span) did not differ across the groups. Likewise, verbal passive memory skills (forward digit span) were not shown to be superior in any particular group. As with results from the main hypothesis, these results were not confounded by age, education, alcohol consumption, smoking status, or feelings of depression or anxiety.

The last hypothesis predicted that the severity of CKD would be proportional to the extent of cognitive impairment, meaning that all measures used would decline as eGFR (the primary measure of CKD) declined. Provided this hypothesis was correct, it would also be expected that uncorrected error rate in the anti-saccade task would be predictive of performance in the neuropsychological measures. This hypothesis was tested as current literature is conflicting regarding whether or not cognitive function declines in accordance with CKD stage, rather than decline between pre-dialysis CKD and haemodialysis CKD.[105] Subsequently, it was found that years of education were predictive of uncorrected error rate, rather than severity of CKD with small to moderate effect size (β = -.36). The hypothesis was largely unsupported by the remainder of results obtained from the neuropsychological measures. Stage of disease was only indicative of how long CKD participants took to complete the Stroop task. However, in this model, age was found to have a larger effect size than stage of disease (β = .64 in age, β= -.34 in eGFR) and is likely to be more predictive of time taken to complete the Stroop.

Although, it was found that uncorrected error rate in the anti-saccade task was the only covariate that predicted the reverse digit span score and total errors in the Stroop task, implying that uncorrected error rate in the anti-saccade task is predictive of inhibitory control and complex working memory functions in CKD. The uncorrected error rate was also indicative of forward spatial span score, in addition to age, with small effect sizes (uncorrected error rate β = -.28, age β = -.29). Additionally, reduced global cognition and a lower IQ was resultant of less years spent in education with moderate to large effect sizes (β = .4 in ACE-R and β = .54 in the NART) rather than stage of CKD. The remainder of the neuropsychological measures (forward digit span, reverse spatial span, uncorrected error rate of Stroop task) were not found to be predicted by severity of CKD, uncorrected error rate in the anti-saccade task, or any demographic covariates, but rather by unknown alternative covariates.

In summary, anti-saccade task and cognitive performance largely appeared to be better in control participants compared to participants that were receiving haemodialysis. Additionally, performance in some of the neuropsychological measures was poorer in CKD participants compared to controls also. However, the results from the third hypothesis suggested that anti-saccade uncorrected error rate was predictive of complex verbal working memory and attentional control (holding information, manipulating it for a certain task), and verbal inhibitory control. Although, results from the third hypothesis indicated that others factors, such as age or years of education may be more predictive of overall cognitive status in the CKD groups of this study.

5.2 Anti-saccade uncorrected error rate

The main hypothesis of this study indicated that HD participants would have the highest uncorrected error rate in the anti-saccade task, followed by the CKD group and that controls would exhibit the lowest uncorrected error rate. Crawford et al's[4] initial study in 2005 found that participants with early Alzheimer's disease made ten times more uncorrected errors in the anti-saccade task compared to matched controls.[4] The results of the central hypothesis of this study were consistent with Crawford et al's study.[4] It was found that participants receiving haemodialysis made six-times more uncorrected errors than the control population, while the pre-dialysis participants made around three-times more uncorrected errors than controls. However, uncorrected error rate in the anti-saccade task did not appear to differ between the pre-dialysis population and dialysis population following post-hoc testing. There was, however, a difference between the control population and HD population. Before this is discussed further, the lack of performance difference in uncorrected error rate between the CKD and HD group, and the CKD and control group should be considered.

It is likely that there was no difference in uncorrected error rate in the CKD group when compared to the controls and haemodialysis populations as both early and late stage CKD patients were situated into one participant group. This means there was little discrimination between test performance of early and late stage CKD patients. In fact, seven of 22 CKD participants (32%) were in 'late' stages (stage 4 or 5) of CKD. This may explain why there was no significant difference between performance in the anti-saccade task between the CKD group and HD group. Similarly, five of 22 CKD participants (22%) had 'early' stage CKD (stage 1 or 2). Equally, this may also account for why there was no difference in performance between the control and CKD group. Current literature suggests participants in earlier CKD stages have less severe CI symptoms than later stage participants due to a combination of worsening 'uraemic' symptoms, higher risk of subclinical neurovascular disease and reduced feelings of 'alertness' as CKD progresses.[1, 15, 25] Individuals receiving haemodialysis are exposed to more of these risk factors for CI than those in earlier stages of CKD. For example,

the process of haemodialysis itself is considered and independent risk factor for impairment; with those receiving dialysis for a longer period of time are more likely to develop CI.[1] Considering this, it is unsurprising that the haemodialysis group exhibited a worse performance than the control group in the anti-saccade task.

In summary, it was found that haemodialysis patients had a higher uncorrected error rate than the control group. This is likely to be due to the fact that individuals receiving haemodialysis are a 'high risk' group in terms of developing cognitive impairment. The results did not indicate that non-dialysis CKD participants performed worse than controls or better than the haemodialysis group as expected. However, this is likely due to the aforementioned limitations of the study.

5.3 Neuropsychological battery performance

The second hypothesis indicated that performance in the neuropsychological battery would decrease as severity of disease increased; HD participants would perform the worst across all measures, CKD participants would perform better than the haemodialysis group, and the controls would exhibit the highest performance level.

The results in the battery support the hypothesis to a degree as performance did not decline across the three groups in any of the measures. However, in four of the nine measures used, it was found that controls exhibited a higher cognitive performance than both experimental groups. This was shown in Addenbrooke's cognitive exam (global cognition), the NART (pre-morbid IQ), the reverse digit span (executive function and working memory), and in the time taken to complete the Stroop task (executive function; psychomotor speed). In total errors of the Stroop task it was shown that the control group achieved a higher performance than the HD group. No group exhibited a higher performance level over any other group in the forward digit span (passive, verbal memory), forward and reverse digit span (passive visuospatial memory and working memory), and uncorrected error rate in the Stroop task. It was likely that

performance did not differ between the two experimental groups in any of these measures as pre-dialysis participants in different stages of chronic kidney disease were situated in one group. With this in mind, it is likely to be of more clinical value to identify what percentage of participants in each group were cognitively impaired according to the arbitrary 'cut-off' scores each of the measures used. Additionally, the scores attained by participants in the current study will be compared to scores achieved by other CKD and HD populations in different studies to assess the generisability of results.

5.3.1 ACE-R

Four of 22 CKD participants (18%) and six of 22 HD participants (27%) were globally impaired in this study according to the ACE-R cut-off value (88 points or less out of 100). When compared to current literature, no other study with a CKD population used Addenbrooke's cognitive exam to assess global cognition. However, other reliable measures were used with similarly good construct validity to the ACE-R, i.e. the 3MS. These studies found that prevalence of cognitive impairment in these measures varied between 10-16% of both pre-dialytic and dialysis participants, which is similar to this study.[37, 87, 105] This figure was comprised predominantly of haemodialysis participants and late stage chronic kidney disease participants.

5.3.2 NART

This study's CKD and HD population was mostly shown to have high IQs according to the National Adult Reading Test (NART). For example, fourteen CKD participants (64%) and ten HD participants (45%) had a 'high average' IQ. Only one study published raw participant scores of the NART Agganis et al[39] found that the mean IQ of 241 participants (mean age

63.8 years) was 102 which is considered to be an 'average' score according to the Weschler Adult Intelligence Scales.[39] As shown in table 7, the mean IQ scores in our control and experimental groups were higher (*M* = 118 in controls, *M* = 114 in CKD , *M* = 110 in HD). This may have impacted performance of CKD and HD participants in other neuropsychological measures in that cognitive function was better in this study population, compared to the wider CKD and HD population. This is discussed further with results obtained from the third hypothesis (see page 86).

5.3.3 Digit span

A smaller proportion illustrated poorer performances the forward digit span; two of 22 CKD participants (9%) and none of the HD participants were found to be impaired in this measure of 'passive', verbal short term memory by achieving a 'poor' score as indicated by the Wechsler Adult Intelligence Scale (six points or less).[123]

A higher number of participants were impaired in the reverse digit span. This measure assesses executive function and working memory; the ability to acquire and maintain 'new' verbal information in the mind, then the ability to manipulate this information in order to achieve a task goal. A score of five points or less indicates impairment in this ability. Five of 22 CKD participants (27%) and seven of 22 HD participants (32%) were found to be impaired in this measure. The forward and reverse digit spans have been used in both CKD and HD populations. However, the raw scores in these measures of the study population were only published in two studies.[90, 101] One of these studies assessed both CKD and HD participants that had a mean participant age of 61.2 years. Both of these participant groups had a mean score of seven points in the forward digit span and six in the reverse digit span, which are lower mean scores than this study's participant groups (see table 7, page 72).[90, 101]The other study assessed HD participants and controls, with a mean age of 58 years and a mean score of

seven in the forward digit span and six in the reverse digit span.[90] Again, this is a lower score compared to this study's HD participant group (see table 7, page 72). This implies that the current study's population has better short term verbal memory skills, and verbal working memory skills compared to other people with CKD/receiving HD.

5.3.4 Spatial span

The spatial span is the visuospatial counterpart of the digit span. The forward spatial span is a 'passive' measure of short term visuospatial information. A score of six points or less is indicative of impairment in this measure. Seven CKD participants (32 %) and eleven HD participants (50%) were impaired in this ability. A higher number of participants were impaired in the reverse spatial span than in the forward spatial span. The reverse spatial span measured executive functioning and working memory, specifically, the ability to retain 'new' information and rearrange this to perform a task. A score of five points or less is indicative of impairment in this measure. Seven of 22 CKD participants (32%) achieved five points or less, and 13 of 22 HD participants (59%) had a score indicative of impairment. The mean scores of the forward and reverse spatial span were also compared to results in the literature. However, only one study published the raw scores of CKD and HD participants for the forward and reverse digit span. The mean age of all participants in this study was 61.2 years which is similar to the current study.[101] The mean score of the forward spatial span was seven for both CKD groups, and the mean score of the reverse spatial span was six and five in CKD and HD participants, respectively.[101] This is the same as the mean scores our study population obtained in these measures (see table 7, page 72), implying that this study population's visuospatial skills are similar to other people with CKD/receiving haemodialysis.

The study that provided raw scores of both the digit and spatial span in a CKD and HD population found that 18% of participants had impairment of working memory based on digit span and spatial span scores.[101] This study's population of CKD participants with impairment

in working memory in these measures was 55% (24 participants of 44 CKD and HD participants).

5.3.5 Stroop task

There were no 'cut-off' values for the measure used in the Stroop task. However, as controls performed the task faster than the experimental groups, it is implied that psychomotor speed was slower in the CKD and HD groups. Interestingly, although the HD participants made the most errors in the Stroop task. However, there was subsequently no difference in uncorrected error rate of the Stroop task between the groups. This implies that while inhibitory control was reduced in the HD group, ability to self-monitor and correct errors did not differ between the groups. As previously mentioned, the Stroop measure used in this study was not a standardised measure. However, all of the studies that utilised the Stroop task did not publish raw mean scores expect one.[101] This version was shorter (20-30 words) than the measure used in this study, and so the mean time taken to complete the task was not compared. However, all seven studies that utilised the Stroop found that it took participants with CKD significantly longer to complete than controls implying that other CKD and HD study populations have a slower psychomotor speed compared to the general population, as with the participants in this study.[38, 80, 83, 88, 90, 99, 101, 104]

Overall, these results indicate that there is a higher prevalence of executive dysfunction and reduced working memory abilities in CKD and haemodialysis participants over any other type of impairment. This is consistent with other studies, as shown above. However, there are some factors that must be taken into consideration. It is likely that the prevalence of cognitive impairment in this population is lower than that of the wider CKD population for a number of reasons. Firstly, the participants in the current study are comparatively young (M = 59.1 years) compared to participants in other studies, thereby the prevalence of cognitive impairment

would naturally be lower. Although the results in some measures used in this study were compared to three other studies with similar age groups, these studies are not reflective of the age demographics in the literature. Secondly, according to the NART, the mean IQ scores across both the CKD and HD participant groups were classified as 'high average' scores. The study that this value was compared to highlighted that their participants' mean score was classified as 'average'.[39] Although there is only one study with which to compare these findings, the overall performance level in the current study's population is likely to be quite high as a majority of the participants had above average IQ levels. Similarly, this is likely to be partially due to educational attainment in this study's population also. The mean years of education in other studies' participant groups was mostly between eight to ten years, whereas in the current study CKD participants have completed 14.5 years of full time education and the HD group have completed 14.6 years.[15, 80, 81, 104] The combination of these factors probably positively influenced performance effects in some of the measures utilised in this study, as discussed below.

5.4 Dose-dependent relationship

The third and final hypothesis indicated that eGFR would decline in accordance with cognitive performances in the neuropsychological battery and the anti-saccade task. This hypothesis was made in light of the proposition in current literature; the existence of a 'dose-dependent' relationship between severity of CKD and extent of cognitive impairment.[104] Therefore, it was expected that lower eGFR values in all CKD (including HD) participants would be predictive of worse scores in the neuropsychological battery and a higher uncorrected error rate in the anti-saccade task. Similarly, in line with Crawford et al's[4] work in Alzheimer's disease, it was indicated that a higher uncorrected error rate would be predictive of a worse performance in the neuropsychological battery, which was therefore also expected in this study.[4]

Subsequently, it was found that some demographic covariates were predictive of performance in some of the neuropsychological measures, rather than stage of CKD. Years of education was found to be predictive of uncorrected error rate in the anti-saccade task, Addenbrooke's cognitive exam and the NART. Age and uncorrected error rate in the anti-saccade task were both predictive of the forward spatial span. Whereas, age and eGFR were both found to be predictive of time taken to complete the Stroop task. Lastly, uncorrected error rate in the anti-saccade task was found to be predictive of reverse digit span score and uncorrected error rate in the Stroop task.

The combination of results from hypothesis two and three suggest that paper-based measures are a more effective and specific means of detecting cognitive impairment in CKD. These results also indicate that number of years spent in full-time education and age are more reliable predictors of cognitive performance. However, there are some factors that should be considered alongside these views. Although years of education were predictive of uncorrected error rate in the anti-saccade task and global ability (ACE-R), years of education are a constant and unchanging factor in elderly CKD/HD populations, whereas renal function declines and fluctuates over time. Therefore, although it cannot be claimed from the results of this study that renal function is a reliable indicator of cognitive status, it similarly cannot be interpreted that education would be a consistent predictor either. For example, it is unlikely that if people with CKD/ receiving haemodialysis gained more years in full-time education following onset of CKD symptoms that performance in the anti-saccade task and ACE-R would subsequently improve. Therefore, less years spent in education may be better interpreted as a 'risk factor' for cognitive impairment in this study, rather than predictor which potentially can actively improve cognitive performance.

Additionally, years of education and the other demographic trends observed in this study should be stressed in context with the results. The CKD and HD participants generally had a younger mean age with a higher mean educational attainment compared to participants in other studies.[15, 22, 23, 82, 104, 105, 107] Moreover, patients who volunteered to participate were more

likely to have less comorbidities than those who declined to participate (see 'limitations' sections below). Overall, the combination of a younger, highly educated, comparatively 'healthier' and more motivated study population would likely contribute to a higher performance in the anti-saccade task and neuropsychological battery irrespective of renal function if compared to the broader CKD population.

However, it should be noted that despite these demographic trends, uncorrected error rate in the anti-saccade task was found to be predictive of verbal working memory (reverse digit span), executive functioning; self-regulation (Stroop uncorrected error rate), and visuospatial 'passive' memory (forward spatial span) with small to moderate effects sizes. Self-regulation and working memory are abilities that are commonly found to decline in the CKD population over other patterns of impairment.[1, 38, 83] Moreover, decline in these abilities is found to precede global decline and therefore dementia in the CKD population. As the anti-saccade task was found to be predictive of these abilities, it could be hypothesized that the use of the anti-saccade task in larger participants' groups may come to predict risk of dementia based on the decline of these abilities in CKD. While it could be argued that it is simpler to perform these paper-based tasks to calculate the likelihood of dementia risk, the anti-saccade task may still prove to be beneficial for the following reasons;

Very few paper tasks that measure the aforementioned abilities have a good test-retest reliability, and while the anti-saccade task is subject to 'ceiling effects', this is likely be observed to a lesser extent than paper-based tasks of executive functioning or indeed global ability.[131, 152] Additionally, the anti-saccade task is a more acceptable measure as it takes less time to perform compared to a neuropsychological battery and is less invasive, i.e. feels less like a 'test'. Lastly, it should be considered that the results in this study showed there was no difference between controls, a CKD and HD group in uncorrected error rate in the Stroop task which was a verbal measure of self-monitoring, despite this ability being commonly cited as one which is commonly found to be impaired in people with CKD, as well as other components of executive dysfunction.[38, 90, 104] However, it was found that a significant

difference emerged between the HD group and a control group in a visual measure of self-monitoring (uncorrected error rate in the anti-saccade task). This implies that the anti-saccade task is also a subtler measure of this facet of executive functioning in CKD, rather than the Stroop task, and could more reliably detect a decline in this ability which could be indicative of dementia conversion in HD populations.

5.5 Strengths and Limitations

There are a number of notable strengths in this study. This is the first study to utilise the anti-saccade task in the CKD population. Moreover, this study employed a comprehensive neuropsychological battery that examined multiple psychological constructs, which only a few cross-sectional and longitudinal studies have done previously. The exclusion criteria of this study was also a strength, as a number of studies did not exclude/ account for any confounding effects that central-acting medication or mental illness may have upon the cognitive function of the study population; thereby potentially 'inflating' the prevalence of cognitive impairment.

There are also a limitations of the study which need to be noted. Firstly, as this study is a cross-sectional analysis, inferences regarding trends of cognitive impairment in CKD cannot be made. As this study did not examine a larger number of participants in different stages of CKD over time, it is not possible to predict the rate of further cognitive decline, or assess the sensitivity of the anti-saccade task in measuring this. Additionally, as this study was not powered to perform regression analyses, inferences made about predictor variables should be interpreted with caution. A note has been made of effect sizes to inform future work.

A number of factors may have reduced the external validity of the study. The study population was younger (M = 59.1 years) compared to a large number of studies within the literature where mean age of participants was over 65 years of age.[22, 23, 104, 107] Similarly, although

enough people were recruited to participate in the study so it was adequately powered for the main hypothesis, the size of the study's population was relatively small compared to some of the other studies that recruited exclusively from outpatient/in-centre haemodialysis and CKD populations.[2, 38, 87] Equally, it also appeared that the mean number of years spent in full time of education was higher among participants in this study, which may have contributed to a lower prevalence of cognitive impairment (in addition to better performance in the anti-saccade task). In other studies' the mean number years of education appears to be between eight to ten years, whereby in the current study this figure was higher (M =15.1 years).[15, 82, 104] Lastly, there was an element of selection bias during the recruitment process. Haemodialysis and pre-dialysis patients that were older, or had more co-morbidities were more likely to decline recruitment information regarding the study. Likewise, haemodialysis patients were more likely to meet one or more aspects of the exclusion criteria than CKD participants which is why HD participants were recruited from three different centres. The combination of these issues may have reduced generizability of the results to the wider CKD population.

6. Conclusion and future directions

There are some clinically significant findings in this study that could guide further research in the area of oculomotor testing in chronic kidney disease. Firstly, this study lends further support that people with CKD experience impairments in executive functioning and working memory; constructs which underpin the performance of the anti-saccade task. Additionally, this study is representative of the first attempt of applying the anti-saccade task as an indicator of cognitive impairment in chronic kidney disease. Furthermore, it highlighted that HD participants had greater difficulty performing the anti-saccade task compared to people without CKD.

Future longitudinal studies should examine uncorrected error rate over time to establish if there is a correspondence between a higher uncorrected error rate and severity of impairment in both pre-dialytic and dialytic chronic kidney disease. It should be stressed that further research should be carried out in larger and more diverse CKD population, with a larger number of participants in different stages of CKD. In particular, the relationship between the spatial span, digit span, Stroop task and uncorrected error rate should be examined in larger study populations. This would give further evidence regarding whether or not the anti-saccade task is a quick and reliable measure of executive functioning and working memory in people with CKD. Lastly, alternative parameters in the anti-saccade task could be examined. While uncorrected error rate was found to be a specific measure which was indicative of extent of impairment in Alzheimer's disease, alternative parameters may show to be more discriminative against stages of cognitive impairment in chronic kidney disease rather than uncorrected error rate.

7. References

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Appendix 1

Presentations

Preliminary results of this work was used to make a poster presentation at the University of Durham in April 2016, for the Occulomotor Attention and Readiness Workshop.

Appendix 2

Below are the studies which were analysed in the literature review section of this thesis. The citation number that appears in the Reference section is listed beside each study.

Systematic reviews

1. Etgen T, Chonchol M, Forstl H, Sander D. Chronic Kidney Disease and Cognitive Impairment: A Systematic Review and Meta-Analysis. Am J Nephrol. 2012;35:474-82. **(128)**
2. Shen Z, Ruan Q, Yu Z, Sun Z. Chronic kidney disease-related physical frailty and cognitive impairment: a systemic review. Geriatr Gerontol Int. 2016. **(130)**

Cross-sectional studies

Community based

1. Zammit A, Katz M, Lai J, Zimmerman M, Bitzer M, Lipton R. Association Between Renal Function and Cognitive Ability Domains in the Einstein Aging Study: A Cross-Sectional Analysis. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2014;70(6):764-770. **(22)**
2. Zammit A, Katz M, Zimmerman M, Bitzer M, Lipton R. Low eGFR is associated with dysexecutive and amnestic mild cognitive impairment. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;1(2):152-159. **(23)**
3. Kurella M, Yaffe K, Shlipak M, Wenger N, Chertow G. Chronic kidney disease and cognitive impairment in menopausal women. American Journal of Kidney Diseases. 2005;45(1):66-76. **(81)**
4. Kurella Tamura M, Wadley V, Yaffe K, McClure L, Howard G, Go R et al. Kidney Function and Cognitive Impairment in US Adults: The Reasons for Geographic and

Racial Differences in Stroke (REGARDS) Study. American Journal of Kidney Diseases. 2008;52(2):227-234. **(82)**

5. Elias M, Elias P, Seliger S, Narsipur S, Dore G, Robbins M. Chronic kidney disease, creatinine and cognitive functioning. Nephrology Dialysis Transplantation. 2009;24(8):2446-2452. **(83)**
6. Yaffe K, Kurella-Tamura M, Ackerson L, Hoang T, Anderson A, Duckworth M et al. Higher Levels of Cystatin C Are Associated with Worse Cognitive Function in Older Adults with Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Cognitive Study. Journal of the American Geriatrics Society. 2014;62(9):1623-1629. **(84)**
7. Lee J, Chin H, Byun M, Choe J, Park J, Lee S et al. Impaired Frontal Executive Function and Predialytic Chronic Kidney Disease. J Am Geriatr Soc. 2011;59(9):1628-1635. **(85)**

Haemodialysis

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2. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al . Cognitive Impairment in haemodialysis patients is common. Neurology. 2006;67:216-23 **(38)**
3. Jung S, Lee Y, Choi S, Hwang S, Noh J. Relationship between Cognitive Impairment and Depression in Dialysis Patients. Yonsei Medical Journal. 2013;54(6):1447. **(37)**

4. Kurella-Tamura M, Larive B, Unruh M, Stokes J, Nissenson A, Mehta R et al. Prevalence and Correlates of Cognitive Impairment in Hemodialysis Patients: The Frequent Hemodialysis Network Trials. Clinical Journal of the American Society of Nephrology. 2010;5(8):1429-1438. **(87)**

5. Post J, Morin K, Sano M, Jegede A, Langhoff E, Spungen A. Increased Presence of Cognitive Impairment in Hemodialysis Patients in the Absence of Neurological Events. American Journal of Nephrology. 2012;35(2):120-126. **(88)**
6. Dixit A, Dhawan S, Raizada A, Yadav A, Vaney N, Kalra O. Attention and information processing in end stage renal disease and effect of hemodialysis: a bedside study. Renal Failure. 2013;35(9):1246-1250. **(89)**
7. Tiffin-Richards F, Costa A, Holschbach B, Frank R, Vassiliadou A, Krüger T et al. The Montreal Cognitive Assessment (MoCA) - A Sensitive Screening Instrument for Detecting Cognitive Impairment in Chronic Hemodialysis Patients. PLoS ONE. 2014;9(10):e106700. **(90)**
8. Wolfgram D, Sunio L, Vogt E, Smith H, Visotcky A, Laud P et al. Haemodynamics during dialysis and cognitive performance. Nephrology. 2014;19(12):771-776. **(91)**
9. Schneider S, Malecki A, Müller K, Schönfeld R, Girndt M, Mohr P et al. Effect of a single dialysis session on cognitive function in CKD5D patients: a prospective clinical study. Nephrol Dial Transplant. 2015;30(9):1551-1559. **(92)**

Pre-dialysis CKD

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2. Jassal S, Roscoe J, LeBlanc D, Devins G, Rourke S. Differential impairment of psychomotor efficiency and processing speed in patients with chronic kidney disease. Int Urol Nephrol. 2008;40(3):849-854. **(93)**
3. Kurella Tamura M, Xie D, Yaffe K, Cohen DL, Teal V, Kasner SE, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. Clin J Am Soc Nephrol. 2011;6(2):248-56 **(94)**
4. Williams U, Owolabi M, Ogunniyi A, Ezunu E. Prevalence and Pattern of Neurocognitive Impairment in Nigerians with Stages 3 to 5 Chronic Kidney Disease. ISRN Neurology. 2013;2013:1-6. **(95)**
5. Yeh Y, Huang M, Hwang S, Tsai J, Liu T, Hsiao S et al. Association of homocysteine level and vascular burden and cognitive function in middle-aged and older adults with chronic kidney disease. Int J Geriatr Psychiatry. 2015;31(7):723-730. **(96)**
6. Yeh Y, Huang M, Liang S, Hwang S, Tsai J, Liu T et al. Indoxyl sulfate, not p-cresyl sulfate, is associated with cognitive impairment in early-stage chronic kidney disease. NeuroToxicology. 2016;53:148-152. **(97)**
7. Egbi O, Ogunrin O, Oviasu E. Prevalence and determinants of cognitive impairment in patients with chronic kidney disease: A cross-sectional study in Benin City, Nigeria. Ann Afr Med. 2015;14(2):75. **(98)**
8. Silverwood RJ, Richards M, Pierce M, Hardy R, Sattar N, Ferro C, et al. Cognitive and kidney function: results from a British birth cohort reaching retirement age. PLoS One. 2014;9(1):e86743. **(103)**

HD and pre-dialysis

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2. Post J, Jegede A, Morin K, Spungen A, Langhoff E, Sano M. Cognitive Profile of Chronic Kidney Disease and Hemodialysis Patients without Dementia. Nephron Clinical Practice. 2010;116(3):c247-c255. **(99)**
3. Sánchez-Román S, Ostrosky-Solís F, Morales-Buenrostro L, Nogués-Vizcaíno M, Alberú J, McClintock S. Neurocognitive Profile of an Adult Sample With Chronic Kidney Disease. Journal of the International Neuropsychological Society. 2010;17(01):80-90. **(100)**
4. Seidel UK, Gronewold J, Volsek M, Todica O, Kribben A, Bruck H, et al. The prevalence, severity, and association with HbA1c and fibrinogen of cognitive impairment in chronic kidney disease. Kidney International. 2014;85(3):693–702. **(101)**
5. Nasser Mel T, Shawki S, El Shahawy Y, Sany D. Assessment of cognitive dysfunction in kidney disease. Saudi J Kidney Dis Transpl. 2012;23(6):1208-14. **(102)**

Comparison of a haemodialysis group and transplant group

1. Anwar W, Ezzat H, Mohab A. Comparative study of impact of hemodialysis and renal transplantation on cognitive functions in ESRD patients. Nefrología (English Edition). 2015;35(6):567-571. **(79)**

Longitudinal studies

Community studies

1. Kurella M. Chronic Kidney Disease and Cognitive Impairment in the Elderly: The Health, Aging, and Body Composition Study. Journal of the American Society of Nephrology. 2005;16(7):2127-2133. **(15)**
2. Davey A, Elias M, Robbins M, Seliger S, Dore G. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. Nephrology Dialysis Transplantation. 2012;28(7):1810-1819. **(86)**
3. Seliger S. Moderate Renal Impairment and Risk of Dementia among Older Adults: The Cardiovascular Health Cognition Study. Journal of the American Society of Nephrology. 2004;15(7):1904-1911. **(104)**
4. Slinin Y, Paudel M, Ishani A, Taylor B, Yaffe K, Murray A et al. Kidney Function and Cognitive Performance and Decline in Older Men. Journal of the American Geriatrics Society. 2008;56(11):2082-2088. **(105)**
5. Etgen T, Sander D, Chonchol M, Briesenick C, Poppert H, Forstl H et al. Chronic kidney disease is associated with incident cognitive impairment in the elderly: the INVADE study. Nephrology Dialysis Transplantation. 2009;24(10):3144-3150. **(106)**
6. Buchman A, Tanne D, Boyle P, Shah R, Leurgans S, Bennett D. Kidney function is associated with the rate of cognitive decline in the elderly. Neurology.2009;73(12):920-927. **(107)**

7. Helmer C, Stengel B, Metzger M, Froissart M, Massy Z, Tzourio C et al. Chronic kidney disease, cognitive decline, and incident dementia: The 3C Study. Neurology. 2011;77(23):2043-2051. **(108)**
8. Feng L, Yap K, Yeoh L, Ng T. Kidney Function and Cognitive and Functional Decline in Elderly Adults: Findings from the Singapore Longitudinal Aging Study. Journal of the American Geriatrics Society. 2012;60(7):1208-1214. **(109)**
9. Jassal S, Kritz-Silverstein D, Barrett-Connor E. A Prospective Study of Albuminuria and Cognitive Function in Older Adults: The Rancho Bernardo Study. American Journal of Epidemiology. 2010;171(3):277-286. **(110)**

Haemodialysis populations

1. Bossola M, Antocicco M, Di Stasio E, Ciciarelli C, Luciani G, Tazza L et al. Mini Mental State Examination over time in chronic hemodialysis patients. Journal of Psychosomatic Research. 2011;71(1):50-54. **(111)**
2. Harciarek M, Williamson J, Biedunkiewicz B, Lichodziejewska-Niemierko M, Dębska-Ślizień A, Rutkowski B. Risk Factors for Selective Cognitive Decline in Dialyzed Patients with End-Stage Renal Disease: Evidence from Verbal Fluency Analysis. Journal of the International Neuropsychological Society. 2011;18(01):162-167. **(112)**

ESRD and pre/post transplant

1. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, Dębska-Ślizień A, Rutkowski B. Continuous cognitive improvement 1 year following successful kidney transplant. Kidney International. 2011;79(12):1353-1360. **(113)**

Appendix 3

Below is the information sheet sent to potential participants. Phone numbers and email addresses have been removed.

INFORMATION SHEET FOR PARTICIPANTS

(PATIENTS)

Saccadic Eye Movements as an early indicator of cognitive impairment in patients with Chronic Kidney Disease

PRINICIPAL INVESTIGATOR

Dr Trevor Crawford

Senior Lecturer, Fylde College
Lancaster University
Lancaster LA1 4YF
Tel: ******

Patient ID number:

Why have I been chosen to participate?

You have been chosen because you are a renal patient and this is sometimes associated with confusion or forgetfulness. Doctors do not yet fully understand the causes of these symptoms and so struggle to decide who may or may not develop them. This research is being done to understand whether a better diagnosis could be given if eye movements were used as a way of examining how the brain is functioning.

What is the purpose of the study?

People with Chronic kidney disease may experience difficulty in remembering things and they may feel that their mind is not as sharp as it was before the illness. The aim of this project is to understand more about these effects in pre-dialysis and dialysis renal patients by testing two types of eye movements. These are called 'reflexive' and

'volitional' eye movements, and they provide a simple measure of how well the brain controls our attention so that we can move our eyes towards or away from visual information. We would like to see if these eye movements are linked to mild cognitive symptoms in renal patients. This research will be used to gain an M.Sc degree as part of the medical student's training programme at Lancaster University.

What will be expected of me if I decide to participate?

If you agree to participate in this research study, the following will be expected of you:

1. In the testing room you will be presented with a series of short visual tasks on a display screen. In each task you will see on the screen a central light to look at. After a short time this light will disappear and a new light will appear either to the left or the right of the original central light. In the first part of the test you will be asked to look quickly and accurately towards the single light on the display. In the second part of the test you will be required to look in the opposite direction to the light. In the third test a red and green light will appear on the screen. You will be asked to look towards the red light and to ignore the green light.
2. In order to record accurately your eye movements you will be asked to wear an elasticated light headset in a plastic frame around your head. This will allow you to see the lights clearly. This headset contains the eye tracker that will follow your eyes while you are looking at the lights.
3. You will also be asked to complete several tasks that test your memory and attention. This will involve a series of simple questions. These will provide more information to help us identify whether the eye movements are related to other functions of the brain.
4. You will receive feedback on the tests as the scores will be readily available afterwards. Although we will also provide you with general feedback about the accuracy of the eye tracking results, we will not be able to give you comprehensive feedback as the complete eye movements will take much longer to be processed. The tests will take around 30-35 minutes. (Note: Eye movements are analysed on the laboratory computers offline, with specialist software and takes 1 hour per participant.)

Is the study confidential?

Your personal information will be kept secure and separate from the data sheets gathered. This ensures that your personal information will remain confidential. A special study code will be assigned to you: your name will not appear on study forms and you will not be identifiable in the results of the study. If you agree to take part in the research your medical records may be inspected by the regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed.

What are the risks of participating in the study?

Participation in this study involves minimal risk. The nature of the study requires that you wear an adjustable headset which has two small infra-red emitting cameras attached in order to monitor your eye movements throughout the study. The headset can be removed at any time if you feel that it is becoming uncomfortable. You will be asked to sit with your chin resting on a chin rest while you are looking at the lights. There will be regular breaks during the session. If at any point you become tired you should inform the researcher who will allow you to have additional rest periods as required.

What are the benefits of participating?

Your participation will help in understanding how common, and how severe are the changes in mental abilities in renal patients. By participating in this research you will help the investigators to understand:

- more about the pathways involved in mental abilities
- how these could lead to significant problems in the long term
- ways to maintain and improve the remaining skills.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. You will still be free to withdraw at any time and without giving a reason. Your decision, whether or not you wish to take part, or should you wish to withdraw at any time, will not affect the standard of care you receive.

Will it cost me anything?

Participation in this research study involves no cost to you. You will not be paid or compensated for your participation. However, we will be contributing towards your travel costs.

Who is funding and sponsoring this study?

This study is funded by University Hospitals of Morecambe Bay NHS Foundation Trust and Lancaster University.

What will happen to the results of the research study?

The data gathered from you and all the other participants in the study will be analysed and published in a medical journal. The results may also be presented at conferences and used to support future medical research. It will contribute to our understanding of the mental abilities in kidney patients. This research may also help us to diagnose diseases much earlier and to monitor the effects of new treatments.

Will the eye tracking and cognitive results be stored for future use in this research study?

Yes, if you agree to this. Chronic Kidney Disease is a disease of ageing. This means that the symptoms can develop over a long period of time. In order to track the development of the disease and to measure the changes in the symptoms we will need to conduct longitudinal studies over many years on both affected and non-affected participants. We also need to assess people at different stages in the development of disease. When we have finished recruiting all participants and completed our analyses we will publish our findings in a medical journal, but individual participants will not be identified.

Will the researchers require access to my medical records?

Yes if you agree. In order to help us understand the causes of your symptoms we will need some information that may be contained in your medical records about any events or previous illnesses and medications that have preceded these symptoms. We will also need some information about your education and work history.

Does my GP need to know that I will be in the study?

It is important for your GP to know that you are participating in a research study. We will ask you whether you are happy for them to be informed of this. You will not need to inform your GP, as we will do this for you.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. You should ask to speak with the researchers who will do their best to answer your questions (Dr Jane Simpson, ***** ******). If you remain unhappy and wish to complain formally, you can do this by contacting Professor David Allsop, Professor of Neuroscience, Faculty of Health & Medicine, Lancaster University, LA1 4YG. Tel ***** ********.

Who has reviewed the study?

This grant application was both internally and externally reviewed. The internal expert peer review was conducted according to standard Lancaster University procedures. The research project was approved by Head of department and the Faculty of Science and Technology Research Office. The project was reviewed by two international experts and their comments were provided to the funding organisation's Board of Trustees. The study has been reviewed by NRES Committee East Midlands - Nottingham.

Contact information and questions about the study:

If you have any questions about the study at any time you can contact by telephone or email (below). Contacting any of the team for information does not equate to consenting to participate.

Ms Dearbhla Cosgrove
Dr. Trevor Crawford
Dr. Jane Simpson

Thank you very much for taking the time to read this information sheet. The study is sponsored by Lancaster University. If you would like to discuss any aspect of this research with someone who is not connected with this work, but has relevant research expertise please contact: Dr ******** email address **********@lancaster.ac.uk. Psychology Department, Research administrator, Lancaster University.

Appendix 4

The consent form given to CKD and HD participants is shown below.

Study Number:

Consent Form
Title of Project: Saccadic Eye Movements as an early indicator of cognitive impairment in patients with Chronic Kidney Disease

Name of Researchers: **Dr A Ahmed** **Dr T Crawford**

Please initial box

I confirm that I have read and understand the information sheet dated……
(version .....) for the above study. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

I understand that relevant sections of any of my medical notes and data collected during the study may be viewed by responsible individuals from Lancashire Care NHS Trust, from regulatory authorities where it is relevant to this research. I give permission for these individuals to have access to my records. ☐

I understand that relevant sections of any of my medical notes may be viewed by members of the research team from University Hospitals of Morecambe Bay NHS Foundation Trust and Lancaster University where it is relevant to this research. I give permission for these individuals to have access to my records. ☐

I agree to my GP being informed of my participation in the study. ☐

I agree for my eye movement and cognition scores to be stored for future use in this research study ☐

I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature
_____	_____	_____
Name of Person taking consent (if different to researcher):	Date	Signature