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Cognitive functioning and psychological distress in patients with liver disease

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Chapter 1

Introduction

Approximately 1% of all reported deaths in South Africa are as a result of end stage liver disease (ESLD). ESLD can result from infectious diseases (viral hepatitis), excessive drug and alcoholic use (including pharmaceutical drugs such as paracetamol), metabolic diseases (Wilson's disease) and choleastatic diseases (Suriawinata & Thung, 2011). The current treatment method for patients with ESLD is to undergo a liver transplant (LT.)

Advanced ESLD is far from being an isolated disorder of the liver as it has notable consequences for the body and on brain functioning (Vilstrup et al., 2014). The alteration in brain functioning, which produces changes in cognitive, behavioural and motor effects is termed Hepatic Encephalopathy (HE) (Vilstrup et al., 2014). HE, a frequent complication of ESLD, refers to a progressive neuropsychiatric disorder which encompasses a clinical spectrum of symptoms involving psychomotor, intellectual, cognitive, and motor function. MHE is part of the spectrum of HE. Patients with MHE do not present with observable clinical signs of HE on neurologic examination. Rather, MHE incorporates subtle changes in attention, psychomotor speed and executive decision making (Randolph et al., 2009). For patients and caregivers alike, MHE can be debilitating with significant negative effects on activities of daily living such as work, driving and quality of life (QoL) (Kappus & Bajaj, 2012).

The standard protocol for international hospitals that perform LTs involves a comprehensive physiological, psychological and neuropsychological pre-LT evaluation of a patient diagnosed with LD (Blei, Cordoba & Am. Coll. of Gastroenterology, 2001). Despite neuropsychological assessment being the only method of detecting MHE, the vast majority of

hospitals in South Africa, apart from the Wits Donald Gordon Medical Centre Transplant Clinic (WDGMC), are not known to include this as part of their standard evaluation. The importance of ascertaining MHE is motivated through the current literature which has demonstrated an association between this and the risk of overt hepatic encephalopathy (HE) (Teperman, 2013). Furthermore, MHE has been found to be a factor which predicts a patient's chance of survival both pre-LT and post-LT (Amodio et al., 2008; Stewart, Malinchoc, Kim, & Kamath, 2007).

Recent research studies highlighting the prognostic value of MHE suggests that in the absence of treatment, MHE may evolve to overt HE which can advance to a coma or ultimately death (Collie, 2005; Lewis & Howdle, 2003; Sorrell, Zolnikov, Sharma, & Jinnai, 2006). Furthermore, previous studies have acknowledged that unless the underlying ESLD is successfully treated, HE has been associated with poor rate of survival and a high risk of recurrence. The current study, firstly, aims at examining the progression of MHE in a select group of patients at the WDGMC who are currently on the waiting list for a LT.

In addition, as a successful LT restores hepatic functioning, previous international studies have highlighted that a LT would similarly reverse the cognitive deficits of MHE. However, as will be seen in the following literature review, a LT does not fully reverse the cognitive deficits of MHE. Therefore, patients who have undergone a LT have residual subtle deficits which affect their quality of life and their daily functioning, such as their ability to drive and work. The second aim of the current study, therefore, is to examine the role of a LT on cognitive functioning in a cohort of patients from the WDGMC.

Thirdly, the present study aims to examine the difference in cognitive functioning for patients who are awaiting a LT and patients who have undergone a successful LT at the WDGMC. Patients who are awaiting a LT are thought to have a worsening cognitive profile due to an

increasing severity of ESLD which occurs whilst the patient is awaiting for a LT. This study shall provide a contribution to the knowledge on the clinical picture of cognitive functioning of patients diagnosed with ESLD in a South African hospital in the hope that attending clinicians will give attention to MHE. Furthermore, due to the limited sample size, the study should be considered as a pilot study and therefore the findings of the study would require additional investigation with a larger, more diverse sample.

The research report will highlight the sampling procedures, instruments, data collection as well as a discussion on the issues pertaining to generalizability and the suitability of the data in the methodology section. Additionally, the methodological section shall draw attention to the analytical procedures which were employed to obtain the results of the research questions are briefly explained. These include namely a one sample t-test, Wilcoxon sign rank tests, an Ancova, a Mann Whitney U Test as well as a Spearman's Rho correlation coefficient.

The analytic section shall report the results in tabular and graphic form which in turn will be discussed to conclude that within the South African context, patients with ESLD suffer from MHE which progressively worsens in the domain of attention. The report shall further conclude that patients who have undergone a successful LT mostly resolve the cognitive impairments of MHE, however, a cognitive deficit remains in visuospatial construction. These results were revealed when the patients who had undergone an LT were compared with patient's awaiting a LT.

Literature Review

This chapter discuss the nature of MHE in patients diagnosed with ESLD and its clinical picture as highlighted by previous research studies. As no previous South African studies have been reported, the literature review draws attention to international research.

Liver Disease

The Role of the Healthy Liver

The liver performs several vital functions which can be divided into four main categories namely: the formation of bile, synthesis, detoxification and metabolism (Bhatia, 1999). Firstly, the liver produces bile which aids in digestion of lipids in the small intestine. Secondly, the liver synthesizes amino acids. For instance, the liver produces serum albumin, a protein found in blood plasma which aids in the clotting of blood. Thirdly, the liver performs the vital role of detoxifying drugs and alcohol. Lastly, the liver accomplishes metabolic alterations through Kupffer Cells (Tarter & Van Thiel, 2001). These cells remove foreign material such as bacteria, proteins and other toxic substances which are harmful in high concentrations (for instance ammonia).

The Diseased Liver

Liver injury is characterised by irreversible cell death due to inflammation (ECAB, 2009). A diseased liver can no longer perform the essential functions of bile production, synthesis, detoxification and metabolism (Bhatia, 1999). Consequently, the lack of bile excretions causes jaundice and gastrointestinal digestive problems in the patient. There is a reduction in protein synthesis and a decreased clearance of drug products leading to the exposure of toxic concentrations of pharmaceutical compounds as well as a disturbance in metabolic function

which leads to an excess of toxins, such as ammonia, manganese and glutamine to accumulate in the blood stream (Marra & Parola, 2011; Wakim-Fleming, 2011).

Etiology of Liver Disease

ESLD can be caused by several factors including an infection, immune system abnormalities, genetically inherited diseases, cancer, steatohepatitis and/or budd-chiari syndrome. The following will describe the common types of ESLD and the types relevant to the research paper.

Infection

Viral hepatitis is the leading cause of liver disease worldwide (Duffy et al., 2014). There is an especially high incidence in developing countries particularly within rural areas. Hepatitis is a viral infection characterized by the inflammation of the tissue cells in the liver (Duffy et al., 2014; Palmer, 2004). There are several types of hepatitis with the most common being hepatitis A, B and C (Palmer, 2004). Hepatitis A, the mildest type, is caused by the hepatitis A virus which is found predominantly in contaminated food, water, faeces and blood (Palmer, 2004). Hepatitis B is caused by the hepatitis B virus transmitted by exposure to infectious bodily fluids such as through sexual intercourse, blood transfusions, the re-use of contaminated needles and syringes as well as from mother to child (Palmer, 2004). Hepatitis B virus and Human Immunodeficiency Virus (HIV) are transmitted via similar routes and are often co-occurring; Boyles and Cohen (2011), for example revealed a prevalence of 7.1% of patients with Hepatitis B virus and HIV in a hospital setting within the Eastern Cape. Hepatitis C is caused by the hepatitis C virus being transmitted through infected blood. Hepatitis C causes scarring of the liver tissue cells which may result in cirrhosis or liver cancer (Palmer, 2004).

Immune system abnormality

LD can be the result of an immune system abnormality such as in autoimmune hepatitis, primary biliary cirrhosis (PBC) and Primary sclerosing cholangitis (PSC). Autoimmune hepatitis is a chronic necro-inflammatory disease of the liver characterised by autoantibodies which mistake normal liver cells for pathogens and subsequently attack them (Zachou, Rigopoulou & Dalekos, 2004). PBC is a chronic autoimmune disease of the liver that damages the bile ducts in which autoantibodies attack the intrahepatic bile ducts so that bile cannot be excreted into the gut and is retained causing further liver damage (Donaldson, 2004). In patients diagnosed with PSC, the bile ducts become blocked due to inflammation and scarring of the liver tissue. PSC may be a result of humoral and cellular immunologic alterations which is characterised by a progressive destruction of the connective tissue which surrounds the intrahepatic and extra-hepatic bile ducts which can result in the development of biliary cirrhosis (Eaton, Talwalkar, & Lindor, 2014; Mendes & Lindor, 2004).

Genetics

Wilsons Disease is a rare genetic disorder located on chromosome 13 in which copper is unable to be excreted from the body. Subsequently, copper accumulates in the tissues of the organs of the body usually beginning in the liver and sometimes followed by the brain. In the event of progression to the brain, Wilson’s disease causes ESLD as well as neurologic and psychiatric symptomology. The initial physical changes in the liver are only visible under a microscope. When hepatitis develops, patients are often thought to have infectious hepatitis or mononucleosis (Brewer, 2001).

Cancer

Liver cancer occurs when the cells in the liver have become malignant due to a virus, alcohol abuse, iron storage disease, aflatoxin, cirrhosis, obesity or diabetes. There are two types of liver cancer namely primary and secondary liver cancer. Primary liver cancer forms in the tissues of the liver. The most common form of primary liver cancer is hepatocellular carcinoma, which begins in the main type of liver cell (hepatocyte). Contrastingly, secondary liver cancer spreads to the liver from another part of the body. Without treatment, liver cancer can also spread into other areas of the body (Curley, 2014).

Steatohepatitis

Non-alcoholic steatohepatitis (NASH) is characterized by an excessive accumulation of fat in the liver without any evidence of other chronic liver disease and an alcohol consumption of less than 20-30 grams per day NASH is largely caused by obesity, type 2 diabetes and hypertension. By way of contrast, Alcoholic Steatohepatitis (ASH) is characterized by an excessive accumulation of fat in the liver and an alcohol consumption of more than 30 grams per day (Scaglioni, Ciccia, Marino, Bedogni, & Bellentani, 2011).

Budd-Chiari Syndrome

Budd-Chiari syndrome is a rare disorder characterized by narrowing and obstruction (occlusion) of the veins of the liver (hepatic veins). The narrowing of veins may occur anywhere from the small and large veins that carry blood from the liver (hepatic veins) to the inferior vena cava (large vein that transports deoxygenated blood from the lower half of the body, including the liver, to the right atrium of the heart). As the blood flow out of the liver is impeded, blood backs up in the liver, causing it to enlarge resulting in scar tissue (Dancygier, 2010).

Liver Transplant

A LT is the preferred treatment option for ESLD and acute liver failure (ECAB, 2009). A LT is a surgical procedure in which a diseased liver is removed and replaced with a healthy liver, or section of the liver, from a donor (ECAB, 2009). The majority of LT operations use deceased organ donors, although, a section of the liver may also be donated from a living donor (ECAB, 2009). Currently, in South Africa, hospitals in Johannesburg (WDGMC) and Cape Town (Groote Schuur Hospital) perform LTs for adults and children (Zuckermann & Loveland, 2012). The WDGMC has performed approximately 200 LTs adults. In 2012 the WDGMC started a pediatric LT program which has performed 59 LT's in the last two years (Laganparsad, 2013; Loveland et al., 2014).

Referred patients are evaluated by a multi-disciplinary team, consisting of hepatologists, gastroenterologists, surgeons, psychologists, social workers, physiotherapists and dieticians. The team determine the severity of the disease, exclude contra-indications, optimize pre-transplant care and candidate condition, educate the patient and family on post procedure implications and ensure that psychosocial circumstances support post-transplant treatment and lifestyle requirements (Zuckermann & Loveland, 2012). Multiple psychosocial issues arise in patients expecting a liver transplant. These include adapting to their changing health and functional capacity, altered social relationships (for instance, no longer being able to drink socially), altered perceptions of the self as well as new life plans and goals. Patients awaiting a LT and their families/caregivers demonstrate better psychological adaption when the entire spectrum of issues are explored (Zuckermann & Loveland, 2012).

Hepatic Encephalopathy

HE is a common complication of ESLD. It is a life threatening and severely debilitating manifestation of ESLD. HE is defined as a spectrum of neuropsychiatric abnormalities in patients diagnosed with ESLD with the exclusion of other known brain disease (Vilstrup et al., 2014). Patients diagnosed with HE exhibit deficits in cognitive functions (such as attention, psychomotor, and fine motor functionality) as well as emotional and behavioral functions.

Classification of HE

HE is classified according to 4 factors: the underlying disease, the severity of the manifestations, its time course and lastly based on the existence of precipitating factors. According to Vilstrup and colleagues (2014) these should be noted during the diagnostic process.

According to the Underlying disease

The 1998 World Congress of Gastroenterology in Vienna states that HE is divided into type A, B and C, contingent on the underlying cause.

- Type A – HE associated with acute liver failure.
- Type B – HE caused by portal-systemic shunting without associated intrinsic liver disease.
- Type C – HE associated with cirrhosis. This is subdivided into episodic (precipitant-induced), persistent (chronic encephalopathy) and minimal encephalopathy (alterations in cognitive function in patients who clinically exhibit a normal mental state) (Ferenci et al., 2002).

The clinical manifestations of types B and C are similar whereas type A has distinct features which has been associated with increased intracranial pressure and a risk for cerebral herniation (Vilstrup et al., 2014).

According to the severity of manifestations

The severity of hepatic encephalopathy is graded using the West Haven Criteria (WHC); this is established on the level of impairment of autonomy, changes in consciousness, intellectual function and behavior.

Table 1.1

West Haven Criteria

ISHEN		Level of Consciousness	Neuropsychiatric symptoms	Neurological symptoms
Unimpaired		Normal	None	None
Covert	Grade 0 – minimal	Normal	Abnormal results on established psychometric and neuropsychological tests exploring psychomotor speed and executive functions	None
	Grade I	Slight mental slowing down	Trivial lack of awareness; Euphoria or anxiety; Shortened attention span; Impairment of addition and subtraction; Altered sleep rhythm	Fine motor skills disturbed (impaired ability to write, finger tremor)
Overt	Grade II	Increased fatigue, apathy or lethargy	Disorientation of time; Obvious personality change; Inappropriate behaviour; Dyspraxia; Asterixis	Flapping tremor, ataxia, slurred speech
	Grade III	Somnolence	Semi-stupor; Responsive to stimuli; Confused; Gross disorientation; Bizarre behaviour	Rigor, clonus, asterixis
	Grade IV	Coma	Does not respond to stimuli (including painful stimuli	Signs of increased intracranial pressure

Note. Adapted from Ferenci et al. (2002)

According to its time course

HE is further subdivided according to its time course. The subdivisions include episodic, recurrent and persistent HE (Vilstrup et al., 2014). Episodic HE occurs when there is an isolated decompensation of neuropsychological functioning. Episodic HE is characterized by the abrupt onset of an acute confusion syndrome that includes an impaired mental state,

motor abnormalities and hyperventilation (Cordoba, 2014). The clinical manifestation of episodic HE may fluctuate rapidly and oscillate from mild confusion to a deep coma (Cordoba, 2014). In the cohort of studies led by Cordoba (2014) the majority of patients had no previous significant neurological abnormalities prior to the onset of episodic HE. Recurrent HE refers to bouts of HE that occur with a time interval of 6 months or less (Vilstrup et al., 2014). Persistent HE signifies a constant pattern of behavioural and cognitive deficits which impact negatively on social and occupational functioning (Ferenci et al., 2002; Vilstrup et al., 2014). Persistent HE is further subdivided into overt HE and covert HE (Ferenci et al., 2002).

According to precipitating factors

HE is further subdivided according to the existence of precipitating factors. Precipitating factors are common in episodic and recurrent HE. These include infections, diuretic overdose, unidentified electrolyte disorder, constipation and GI bleeding. These should be actively sought and treated (Vilstrup et al., 2014).

Minimal Hepatic Encephalopathy

The current study focuses on MHE. Traditionally clinicians have regarded MHE as the mildest form of HE. However, some have made a strong case for MHE as a separate category of illness to emphasize the importance of assessing and treating patients with MHE (Ferenci et al., 2002). MHE is characterized by subtle cognitive and motor deficits as well as an impaired health-related quality of life. The term MHE refers to subtle changes in cognitive functioning, cerebral neurochemical homeostasis, cerebral blood flow, metabolism and fluid homeostasis without a presence of overt HE (Tan et al., 2009). Patients with MHE are thought to be cognitively able as the cognitive deficits associated with MHE are not observable clinical neurological symptoms of HE (Dhiman & Chawla, 2009). However, the

subtle subclinical cognitive deficits associated with MHE, such as attention, visual processing and executive functioning are quantifiable through the use of neuropsychological testing (Dhiman & Chawla, 2009). Consequently, the condition is overlooked by doctors who do not consistently include neuropsychological testing in a patient's evaluation (Dhiman & Chawla, 2009). This is problematic as MHE is a highly prevalent complication of cirrhosis (Dhiman & Chawla, 2009; Liu et al., 2004; Oritz, Jacas, & Cordoba, 2005).

It has been well documented that MHE has a subtle but negative impact on a patient's spatial skills, leading to an increased number of falls, a decreased ability to perform complex tasks (such as driving), a difficulty in gaining and maintaining successful employment, as well as a decreased overall QoL. It has been argued that MHE predicts the development of overt HE and is associated with poor survival (Córdoba, 2011; Cordoba et al., 1998). Due to the negative impact on daily living it is imperative to diagnose this condition. Some authors, such as Lockwood (2000) and Oritz and colleagues (2005), have suggested that failing to diagnose MHE should constitute a medical error.

Epidemiology of MHE

The incidence and prevalence of MHE is established in international settings and ranges from 30-80% of all patients diagnosed with ESLD (Dhiman & Chawla, 2009; Liu et al., 2004; Oritz, et al., 2005). Patients diagnosed with MHE are frequently older, have ASH as their etiology of ESLD, have a history of overt HE, have more severe ESLD and have esophagogastric variances (Boyer, Haskal & American Association for the Study of Liver Diseases, 2005; Dhiman & Chawla, 2009).

The prevalence of MHE is dependent on the methods used as well as the clinician specified cut offs of abnormal and normal functioning of cognitive behaviour on neuropsychological tests as currently there is not a specific criteria to diagnose a patient with MHE. Additionally,

in the context of South Africa the prevalence and occurrence of MHE is poorly established due largely to the lack of hospitals incorporating neuropsychological testing in their work up. As far as could be established only the WDGMC is completing neuropsychological testing in their work up of patients diagnosed with ESLD. According to the preliminary data on cognitive functioning at the WDGMC, approximately 40-50% of patients assessed have cognitive deficits consistent with MHE (Sideris, 2014).

Pathogenesis of MHE

Currently, the exact pathogenesis of HE is unknown due to the limitations in the methods available to investigate the brain function and deficient knowledge of the neurobiological basis of behaviour (Cordoba, 2014). However, several hypotheses have been proposed to account for the changes that occur in HE. Presently, it is proposed that the cause of HE is heterogeneous (Butterworth, 2000; Cordoba, 2014; Haussinger & Schliess, 2005). MHE has been found to have a similar pathogenesis to that of HE (Ahboucha & Butterworth, 2008; Lockwood, Yap, & Wong, 1991; Sharma, Sharma, Puri, & Sarin, 2008).

A frequent hypotheses proposes that MHE is caused by substances which in healthy liver functioning are effectively metabolised by the liver. In patients with liver disease these substances (such as ammonia, manganese and glutamine) accumulate in the blood stream (Marra & Parola, 2011; Wakim-Fleming, 2011). The toxins readily cross the blood brain barrier (BBB) causing damage to nerve cells and astrocytes (neuron support cells which maintain the composition of the fluid surrounding the neurons as well as mediate nerve signal transmission between cells) (Butterworth, 2003). Subsequent to the toxic substances entering the neural tissues, neurochemical changes occur that affect several neurochemical pathways (Butterworth, 2010).

Changes in the blood brain barrier

The BBB serves the essential role of separating the circulating blood from the brain thereby protecting the central nervous system through a selective permeable barrier made up of endothelial cells. In patients with ESLD, the BBB undergoes changes so that substances pass to the brain more readily. Neurotoxins, which are describe below, directly mediate the changes in the permeability of the BBB. Although, this is predominantly seen in the later stages of HE and thus far studies have not found changes in the permeability of the BBB in MHE (Hardy & Kleinman, 2007).

Ammonia

Hyperammonemia is considered to be one of the central causes to the development of MHE as it damages astrocytes (Ott & Vilstrup, 2014). Hyperammonemia is an excess of the nitrogenous substance ammonia. Ammonia is a by-product of nitrogen metabolism which originates in the small intestine as a consequence of an enzyme known as glutaminase (Ott & Vilstrup, 2014). The ammonia is absorbed into the hepatic portal circulation and transported to the liver where, in a normal healthy liver, it is metabolised and passed through the urea cycle (Dragonjic, Krtinic, & Dragonjic, 2013; Ott & Vilstrup, 2014). Dysfunction of the liver reduces the capacity of the body to metabolize ammonia which results in hyperammonemia in the blood which crosses the blood brain barrier (Dragonjic et al., 2013). The molecules are metabolised by astrocytes. Astrocytes are abundant constituting approximately 30% of the cerebral cortex and are responsible for physical and nutritional support for neurons, maintaining the integrity of the BBB as well as regulate cerebral blood flow (Dragonjic et al., 2013; Vaquero, Chung, & Blei, 2003).

The brain has limited capacity to remove ammonia crossing the BBB (Butterworth, 2002). The only way to eliminate ammonia from neuron cells is through a reaction mediated by the

enzyme glutamine synthetase. Alzheimer type II astrocytes are the only astrocytes which contain glutamine synthetase. Glutamine synthetase combines with glutamate (an amino acid) to produce glutamine (Butterworth, 2002). An excess of ammonia results in an excess of glutamate and subsequently glutamine which causes reactive astrogliosis (astrocyte swelling) (Rai & Dhiman, 2013; Tanigami et al., 2005).

In patients with HE, the amount of glutamine formed in the brain has been found to be associated with the severity of the ESLD, which indicates that the brain is exposed to increasing levels of ammonia as the disease progresses (Lockwood, Weissenborn & Butterworth, 1997; Butterworth 2002).Glutamate, a neurotransmitter involved in the modulation of learning and memory, has been found to play an essential role in the expression of learning and memory deficits in patients with MHE (Rai & Dhiman, 2013). Alternatively, an excess of glutamine results in decreased blood flow to the brain as well as edema in astrocytes creates intracerebral pressure which leads to cellular death (Brusilow, Koehler, Traystman, & Cooper, 2010; Butterworth, 2002; Kurmi et al., 2008). However, the specific molecular mechanism responsible for the alterations in neuronal genes and expression of astrocytes affecting neurotransmission which have been revealed in studies in HE are currently unknown (Kurmi et al., 2008; Prakesh, Kanna, & Mullen, 2013).

Blood ammonia concentration is not associated to the severity of neurocognitive impairment and therefore, a consensus exists that, although ammonia has a key role in the pathogenesis of MHE and HE, it is not exclusively accountable for the neurocognitive sequalae. Other factors such as systemic inflammation which cumulate and propagate the clinical presentation of MHE and HE (Aldridge, Tranah, & Shawcross, 2014).

Manganese

Manganese, a trace metal, is required for the maintenance of proper functioning and regulation of numerous biochemical reactions, such as the metabolism of carbohydrates, lipids and proteins (Cichoz-Lach & Michalak, 2013; Sidoryk-Wegryzynowicz & Ascher, 2013). Patents with ESLD are unable to excrete manganese through the biliary system and as a result, manganese is transported to the brain as it crosses the BBB and brain-cerebrospinal fluid barriers. In such circumstances, the excess manganese accumulates in the basal ganglia, caudate nucleus and globus pallidas. Manganese neurotoxicity causes mitochondrial dysfunction, disruptions in energy metabolism, inflammation of the glial cells and disruptions in the synaptic transmission and neuroglial communication (Cichoz-Lach & Michalak, 2013).

The excess of manganese deposits also leads to neurological abnormalities which are characterised by abnormal cognitive, psychiatric and motor function. Manganese is thought to be associated with the development of Parkinsonian manifestation of HE, such as tremors (Cichoz-Lach & Michalak, 2013). Its role is however in other neurological manifestations of HE is currently unknown. Patients with ESLD typically present with a hyper intense signal in the globus pallidus that has been attributed to the accumulation of manganese in the basal ganglia. Studies in the role of manganese and HE have found that manganese impairs dopaminergic neurotransmission (Cordoba, 2014).

Systemic Inflammation

Systemic inflammation occurs in response to a variety of clinical issues, such as sepsis. Sepsis is a precipitating state that has a significant role in in the decompensation of ESLD (Cichoz-Lach & Michalak, 2013). Its presence has been found to be a predictor for worsening HE. In response to sepsis, the peripheral immune system communicates with the brain to release of chemokins, proinflammatory cytokines, proteases and inflammatory gene

transcription causing systemic inflammation. The stimulation of cytokines influences the permeability of the BBB and reduces the reactivity of microglial cells.

Systemic inflammation may be an important factor that contributes to the development of MHE as well as its progression to overt HE. As previously mentioned, the severity of MHE has been found to be independent of blood ammonia levels as well as the severity of ESLD. However, markers of inflammation have been found to be significantly higher in patients with MHE than those without MHE. It has been suggested that inflammation plays a synergistic role with ammonia, producing and modulating MHE (Sundaram & Shaikh, 2009).

Neurotransmitters

Neurotransmitters such as dopamine, GABA and serotonin have additionally been revealed to play an essential role in the development of HE. Dopamine contributes to astrocyte swelling and oxidative stress and is therefore a confirmed precipitating factor for MHE (Ding et al., 2013). Excessive dopamine produced from the liver, is absorbed into the blood and crosses the BBB which subsequently inhibits learning and memory formation (Ding et al., 2013). Currently, clinical trial studies have evaluated the use of levodopa (a drug used to treat patients with Parkinson's disease) as a potential treatment for HE (Junker, Als-Nielsen, Gluud, & Gluud, 2014). However a recent review study concluded that more randomised placebo controlled studies are needed before an accurate decision can be made (Junker et al., 2014).

Serotonin, a neurotransmitter widely distributed in the central nervous system (CNS), is essential for the regulation of sleep, circadian rhythm, memory, learning, information processing, mood, temperature regulation, muscle contraction and cardiovascular function (Durand & Barlow, 2015). As serotonin is primarily found in the gastrointestinal tract, the metabolism of serotonin is sensitive to the degree of porto-systemic shunting and

hyperammonemia. This suggests that serotonin has a role in early neuropsychiatric symptoms (Lozeva-Thomas, 2005).

GABA is an inhibitory neurotransmitter which regulates the transmission of information and action potentials by reducing postsynaptic activity inhibiting a variety of emotions and behaviours (Durand & Barlow, 2015). Patients with ESLD have reduced hepatic uptake of GABA which results in an increased activity of GABA in the brain. However, currently only animal models have shown that the direct introduction of GABA to the brain results in a coma similar to that seen in patients with overt HE (Hardy & Kleinman, 2007).

Clinical Presentation of MHE

Attention

Filley (2002) defined attention as the ability to focus selectively on a stimulus, sustaining that focus and shifting it at will. Posner and Petersen (1990) theorised that attention involves three systems, namely: the posterior attention system, the vigilance attention system and the executive functioning attention system. The posterior attention system denotes conscious attention to orientate to an event or a relevant piece of information (Posner & Peterson, 1990). The vigilance attention system denotes achieving and sustaining attention (Posner & Peterson, 1990). Following which, higher executive functions are responsible for orchestrating voluntary actions (Posner & Peterson, 1990). The following higher executive functions are involved: task switching, inhibitory control, conflict resolution, error detection, allocation of attentional resources, and planning (Weissenborn et al., 2005).

Neuropsychological assessment tasks have found that patients with MHE have deficits in all three of the attention systems (Weissenborn et al., 2005). Lockwood et al. (2002) implemented a Fluoro-Desoxy-Glucose-Positron-Emission Tomography (FDG-PET) study of cerebral glucose utilisation in patients with grade 0 to grade I HE compared with control

participants. They found that in patients diagnosed with MHE the glucose utilization of distinct cerebral areas was significantly decreased compared to controls (Lockwood et al., 2002). Affected areas of this study included the dorsolateral prefrontal cortex, the anterior cingulate gyrus, the orbitofrontal cortex, the temporal parietal junction, and the supplementary motor area. As previous functional imaging studies have indicated that attention involves the anterior cingulate gyrus, supplementary motor area, orbitofrontal cortex, dorsolateral prefrontal cortex, and portions of the basal ganglia and the thalamus thus the functional impairment of these regions due to HE causes attentional deficits in patients with HE (Weissenborn et al., 2005).

Visuospatial perception

Several studies reveal that visuospatial construction is impaired in patients with MHE. Visuospatial construction can be defined as the ability to visualize an object as a set of parts or the ability to construct a replica. It is a complex cognitive operation which involves a purely constructional component, visuo-perceptive, attentional and decision making components. It has been hypothesised that poor or atypical location coding abilities contribute strongly to the impaired abilities observed on construction and drawing tasks (Farran & Jarrold, 2005). A study led by Briesbroek et al. (2013) found that the visuoperceptive component is located in the superior temporal lobe, frontal lobe and supramarginal gyrus. The same study, additionally noted that the constructional component is located in the infarct volume in the right inferior, superior parietal, angular and middle occipital cortices (Briesbrock et al., 2005).

Memory

Memory can be categorised in terms of time, content and/or memory function (process of encoding versus retrieval). According to time memory is differentiated between short-term

memory (STM) and long-term memory (LTM). STM covers 1-18 seconds, while LTM has an unlimited duration. Working memory (WM) deals for short intervals of time concerning either new incoming information or retrieved memory. However, concerning categorising memory by content; memory can be differentiated by priming, procedural, perceptual, semantic, and episodic memory (Calabrese & Markowitsch, 2003).

Distinct brain regions have been identified as being involved in the different memory processes. WM appears to be related to the function of the left fronto-parietal cortex and the cingulum, while semantic memory involves a network including different cortical and subcortical regions. Incoming sensory information is first sent to the frontal and parietal cortex for temporary storage. The limbic memory system evaluates the incoming information with regard to its content and compared to former experiences using the Papez circuit. Additionally, emotional aspects of the new information are evaluated via the amygdala, the medial dorsal thalamus, and part of the basal forebrain. Thereafter, the information is stored in LTM, using a system that involves the hippocampus, parahippocampal gyrus, amygdala, and cortical regions (Calabrese & Markowitsch, 2003).

With regard to MHE there is substantial controversy surrounding whether memory is impaired or not (Weissenborn, Heidenreich, Giewekemeyer, Ruckert & Hecker, 2003). In general, psychometric tests applied to study memory function in patients with HE were focused primarily on semantic memory/WM. Since the result in each of the tests depends on attention as well as memory function, frequently there is no way to determine whether attention or memory are impaired.

A study was performed on memory functioning of 45 cirrhotic patients with grade-0 to grade-I HE compared to 52 healthy controls (Weissenborn et al., 2003). The memory test battery consisted of the digit span, Luria's list of words, the recurring figures test, the Rey–

Osterreith-Complex figure test, the picture memory test and the word-figure-memory test. The study found that patients with MHE have deficits in memory, however these were due to deficits in attention and visual perception. Therefore, it is likely that findings of memory are as a result of another cognitive deficit.

Other markers of cognitive dysfunction

In addition to the aforementioned cognitive deficits associated with MHE, patients have exhibited extrapyramidal signs (EPS) and an impairment in motor abilities (Montgomery & Bajaj, 2012). These are likely a result of manganese deposits in the basal ganglia which affect dopaminergic transmission (Montgomery & Bajaj, 2012). Patients with MHE are more prone to the development of EPS (Montgomery & Bajaj, 2012). EPS refers to impaired motor control such as a resting tremor, rigidity, finger dexterity, gait disturbance, abnormal postural stability and abnormal facial expressions (Montgomery & Bajaj, 2012; Sanders & Gillig, 2012). However, Montgomery and Bajaj (2012) state that motor abnormalities are non-specific and thus far studies with a focus on motor abilities and MHE have been subjective.

Differential Diagnosis of MHE

The diagnosis of MHE requires the professional to examine obvious alternatives which cause brain dysfunction. According to Vilstrup and colleagues (2014) the following disorders alter the level of consciousness of a patient and therefore are possible alternatives to MHE:

- Diabetes (hypoglycaemia, ketoacidosis, hypersmolar, lactate acidosis)
- Alcohol (intoxication)
- Drugs (benzodiazepines, neuroleptics, opioids)
- Neuro-infections
- Electrolyte disorders (hyponatremia and hyper calcemia
- Nonconvulsive epilepsy

- Psychiatric disorders
- Intracranial bleeding
- Dementia (primary and secondary)
- Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
- Obstructive sleep apnoea

Many previous research studies which examine the reversibility of MHE have been unsuccessful in controlling for the aforementioned disorders. The current study will exclude patients who have been diagnosed with one of the aforementioned differential diagnoses in an attempt to control for this.

Natural Progression of MHE

As MHE is not presently being established in South African hospitals, barring the WDGMC, numerous patients, who are either waiting for a LT or have not been put on the waiting list as they are not a suitable candidate, are not receiving treatment to improve their cognitive functioning. There is limited research describing the natural progression of MHE (ECAB, 2009; Keshav & Bailey, 2013). The traditional view is that HE progresses from unimpaired cognition (normal clinical examination and psychometric test results) to MHE, to grade I-II to grade III-IV HE (Córdoba, 2011). Romero-Gomez, Boza, Garcia-Valdecasass, Garcia and Aguilar-Reina (2001) found that MHE predicted a subsequent episode of overt HE as 30% of the participants were reported to have overt HE. However, the study did not exclude the participants who did not have MHE (n=29) when running a Spearman's regression analysis and thus the results do not accurately show that MHE predicts overt HE.

Additionally, Das, Dhiman, Saraswat, Verma and Naik (2001) conducted a study on 72 patients with cirrhosis who underwent serial psychometric testing on follow-up visits at 6–8 week intervals. Das and colleagues (2001) found that 40 of their participants had MHE which

predisposed the cirrhotic patient to overt HE. However, their diagnostic criteria for MHE were problematic. They stated that each participant who scores below normal in two or more of the nine psychometric tests employed in their study had MHE (Das et al., 2001). Although there is currently no golden standard of diagnosing MHE, this method of diagnosis has neglected to take into account that many patients may have had test fatigue which likely could have altered the results of the test (Johnson, Lange, Deluca, Korn & Natelson, 1997).

Consequently, a research study, focusing on the effect of the absence of treatment on cognitive functioning needs to be conducted. This research study will employ a limited number of neuro-psychometric tests as well as control for medical conditions that may have an effect on the results of the neuropsychological tests.

Reversibility of MHE with LT

The benefits of a successful LT is that it restores hepatic functioning and normalises blood ammonia concentrations. Originally, it was hypothesised that a LT would significantly reduce the symptoms of MHE if not completely reverse the condition. Although, several studies have investigated the role of LT on cognitive functioning in patients with ESLD, the reported results are contradictory (Mechtcheriakov et al., 2004; Rose & Jalan, 2004). Thus, it is uncertain if the symptoms of MHE are entirely reversible following a successful LT or if residual symptoms persist and impair patients' daily activities and quality of life.

In a study directed by Naegele and colleagues (2000) 8 participants were seen 3-7 months post-LT and were found to have no residual signs of MHE. However, this study implemented MRI techniques. MRI techniques have been found to be less effective in determining and diagnosing MHE (Zhan & Stremmel, 2012). Yet, Weissenborn and colleagues (1995) reported similar findings in their study which employed MRI techniques and neuropsychological testing and MRI techniques to examine the effect of a LT on MHE in a

sample of 50 participants. Nevertheless, the Weissenborn et al (1995) study only included participants with non-alcoholic cirrhosis, consequently excluding a large number of patients who have MHE.

However, more recent perspective studies that have assessed neuropsychological functioning have challenged the notion of the reversibility of MHE. For instance, Mechtheriakov and colleagues (2004) implemented neuropsychological tests to examine visual motor ability, as well as short and long term memory in a sample of 14 participants after a successful LT. They found that there were residual visual motor deficits 21 months post-LT (Mechtcheriakov et al., 2004). Nevertheless, the study did not examine all the symptoms of MHE such as attention and executive functioning.

Garcia-Martinez and colleagues (2011) led a similar study which examined cognitive deficits of 52 patients diagnosed with cirrhosis. The participants completed neuropsychological testing prior to LT and again 6-12 months later (Garcia-Martinez et al., 2011). Although all cognitive indices improved, 13% of patients showed persistent MHE symptoms (Garcia-Martinez, et al., 2011). The researchers did not control for comorbid disorders such as diabetes mellitus (DM) which was found in 10% of their sample (Sigal, Stanca, Kontorinis, Bodian & Ryan, 2006).

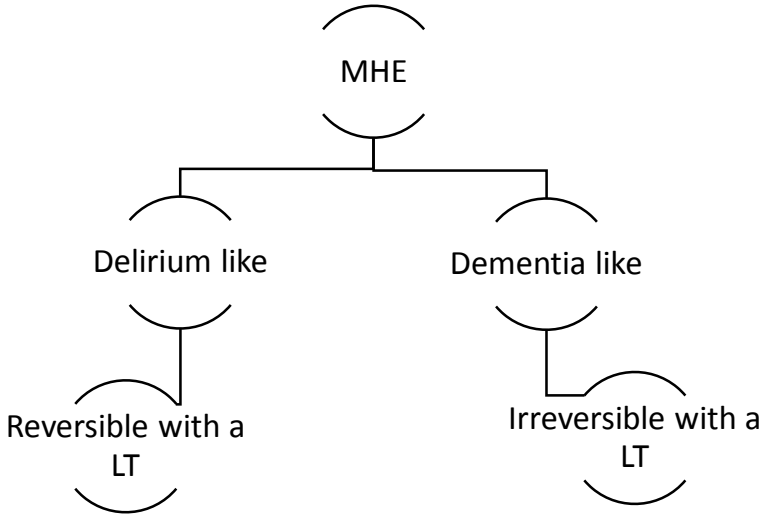
Conversely, Lin and Colleagues (2014) implemented diffusion tensor imaging (DTI) and neuropsychological tests prior to the LT and post the LT on a sample of 28 patients with cirrhosis who had also been diagnosed with HE (Lin et al., 2014). It was revealed that post LT there was decreased water diffusivity which indicates a reversibility in cerebral edema in the left anterior cingulate gyrus, claustrum, postcentral gyrus and right corpus callosum which provided reasoning for a significant improvement in executive functioning and visuospatial functioning (Lin et al., 2014). However, progressive demylination of cells was

found in the temporal lobe providing evidence that MHE is not fully reversible specifically, in memory, language and speech (Lin et al., 2014). However, the paper failed to include the possibility of confounding results which DTI can produce. Therefore, it is questionable whether or not the authors took into consideration the limitations of the imaging technique. Although, DTI is a highly sensitive bio-marker of neuropathology and microstructural changes it is non-specific which is additionally highly sensitive to a broad spectrum of factors such as image noise (both physiologic and thermal), head movement and signal mixing of gray matter, white matter and cerebrospinal fluid which is unavoidable due to the several areas of the brain which have fiber crossings (Alexander, Lee, Lazar, & Field, 2007).

Therefore, Rose and Jalan (2004) claim that the inconsistent findings in reversible MHE following a transplant may suggest that there are two types of MHE (see figure 1.1). MHE manifests clinical features which are consistent with "delirium-like" and "dementia-like" characteristics. Delirium is defined as an acute change in attention and cognition which results in a decreased awareness of the surrounding environment. Dementia is more pervasive and describes a syndrome of decreased intellectual functioning in memory, perception, language and executive functioning. The origin of delirium-like MHE is most likely metabolic whereas the origin of dementia-like is likely to be due to a structural brain lesion caused by ESLD. Reversibility of MHE after a LT would be determined by the underlying pathology rather than a diagnosis on MHE. This proposed hypothesis has neither been confirmed nor refuted as of yet.

Figure 1.1

Proposed Hypothesis



However, it is plausible that rather than there being two different types of MHE, contradictory studies are making use of different testing methodologies. For instance Cordoba's et al (2001), Lin et al., (2014) and Naegele et al. (2000) study which only used MRI techniques found no residual deficits of MHE whereas Garcia-Martinez et al (2011), Mattarozzi et al. (2004), Mechtcheriakov et al. (2004) as well as Tarter et al. (1992), employed either only neuropsychological testing or a combination of neuropsychological testing and neuroimaging techniques revealed that patients with MHE have residual cognitive deficits. It appears therefore, that studies which use imaging techniques to measure the role of a LT on cognitive functioning show an improvement whereas studies which use neuropsychological tests to determine cognitive functioning have found residual deficits in cognitive functioning.

A second incongruence is found in the current literature, which report that there are residual deficits of MHE following a LT, relates to the cognitive domains which show an

improvement compared to those that remain impaired. In the event of different neuropsychological tests being used to identify the syndrome, the probability that different cognitive deficits might be detected in patients with ESLD will increase. Tarter et al. (1992) and Mechtcheriakov et al. (2004) found that the cognitive domain of visuospatial construction remains impaired in patients with cirrhosis. However, Tarter and colleagues (1992) who concentrated their study on a cohort of 62 non-alcoholic patients employed a comprehensive neuropsychological battery of 18 separate tests, revealed an additional residual cognitive deficit in memory. Although both authors used similar tests, such as the Rey Complex figures test, digit symbol test and the trail making test, Tarter et al. (1992) incorporated more measures of memory (such as the digit span test, the Benton visual retention test, the Brown Peterson Test and the Dichotic Numbers test). Tarter et al. (1992) result of a residual deficit of memory could be as a result of a more sensitive test of memory or more likely as an effect of test fatigue. Test fatigue is taken to relate to mental fatigue caused by exhaustive test taking deteriorates the participant's ability to perform mental tasks (Matthews, Desmond, Neubauer & Hancock, 2000).

O'Carroll, Couston, Cossar, Masterton, and Hayes (2003) revealed that in a one year follow up study of 164 patients with ESLD that liver donor recipients showed a significant improvement in all domains with the exception of reaction time when compared with controls. They implemented the Rivermead Behavioural Memory Test and a computerized psychomotor speed test. Lazeyrus et al. (2002) studied 14 patients with cirrhosis (pre-operative MHE (n=8) and no pre-operative MHE (n=6)). They found that patients with pre-operative MHE had persistent mild Parkinsonian symptoms, despite an improvement in other cognitive domains when employing the Trail Making Test (A and B) as well as the Unified Parkinson's Disease Rating Scale. Gracia-Martinez et al. (2011) made use of several tests including Auditory Verbal Learning, Trail Making Test, Symbol Digit Modalities test and the

Grooved Pegboard. They indicated a mild albeit apparent persistence of global cognitive dysfunction in a cohort of 24 cirrhotic patients 6-12 months after LT. Lastly, Hockerstedt et al. (1992) reported that although the majority of neurological symptoms of MHE disappeared after a LT, 50% of the patients showed completely new deficits.

As MHE is not knowingly being established within the South African context (barring the WDGMC), it is impossible to transpose previous international literature with inconsistent findings onto the outlook of cognitive functioning in patients in South Africa who have undergone a successful LT. It is still not clear if the symptoms of MHE are entirely reversible following a LT or if residual symptoms persist and impair a patient's daily activities and quality of life. In the case of persistent residual cognitive deficits following a successful LT, it is impossible to suggest which cognitive deficits show an improvement and which impairments remain or possibly worsen. Further research in this topic is thus required in order to find agreement in conclusions.

Thus, a research study which examines the role of LT on MHE in a sample of participants with all causes of ESLD through neuropsychological testing in all cognitive indices in the South African context is necessary. Neuropsychological testing will be used as it is the most agreed upon form of diagnosing MHE. The ISHEN practice guidelines recommend that in the event of diagnosing and/or studying MHE, clinicians and researchers alike should at least incorporate either the Psychometric Hepatic Encephalopathy score or the Repeatable Battery for the Assessment of Neuropsychological status (RBANs). The present study made use of the RBANs (Ferenci, et al., 2002).

Psychological Distress

In addition to the physiological sequelae, patients diagnosed with ESLD may further have an impaired psychological status which may be a result of one or a combination of the following: a progression of ESLD, disease related complications, restrictions on social life, the need to take drugs and the knowledge of mortality (De Bona et al., 2000). Patients on the waiting list to receive an organ are likely to have fear owing to the uncertainty of the time spent waiting for a liver as well as the awareness of the paucity of organ donations (De Bona et al, 2000; Perez-San-Gregorio, Martin-Rodiguez, Diaz-Dominguez, Perez-Bernal, 2006). Whereas, patients who have had a LT experience psychological distress over accepting a new organ, fears of organ rejection, compliance with stringent immunosuppressant medication, adaption to changed social relationships and occupational settings and sometimes even post-traumatic stress following surgery (Gover & Sarkar, 2012). Additionally, all current pharmacological treatment options of ESLD include medications which have significant side effects. The major side effects are neuropsychiatric (Crone & Gabriel, 2003; Raison, Demetrashvili, Capuron & Miller, 2005). These include fatigue, depression, anxiety, irritability as well as other interpersonal conflicts such as incidences of anger, domestic violence and road rage (Crone, Gabriel & Martini; 2006; Kraus, Schafer, Faller, Csef & Scheurlen 2003; Withers, 2003).

Such psychological reactions complicate the clinical picture with regard to cognition. Dogar and colleagues (2009), Munoz (2008) and Tarter and colleagues (1984), have suggested that psychological symptoms (such as depression, anxiety and paranoid ideation) may have an adverse additive effect on cognitive functioning.

Depression

Depression is a frequent disorder that is associated with ESLD. For instance Munoz (2008) found that 15% of patients with ESLD have depression whereas Guimaro et al. (2011) reported that 45.8 % of their 24 participants had depressive symptoms post-LT. According to the Diagnostic and Statistical Manual 5 (DSM-5), depression can be defined as depressed mood or a loss of interest or pleasure for at least a 2 week period in which there is a change from previous functioning (see Appendix A DSM-5 criteria) (APA, 2013). The symptoms of depression cause clinically significant distress or impairment in social, occupational and/or other areas of functioning. Furthermore, the DSM-5 states the episode is neither due to the effect of a substance or alternative psychological disorder. It is important to note that although patients with ESLD may not be diagnosable with full blown depressive disorder according to the DSM-5 criteria, the patients may show symptoms of the disorder.

Stewart, Enders, Mitchell, Felmlee-Devine and Smith (2011) as well Munoz (2008) indicated that the cause of depression in patients with ESLD may be associated to the pathophysiologic mechanism of MHE itself. Consequently, changes in neurotransmitter activity may potentially lead to mood alterations. Several articles have documented that patients with MHE and depressive symptomatology experienced worsened cognitive profiles than patients without depressive symptomatology (Munoz, 2008; Bianchi et al., 2005; Katon, 2003). This is for the reason that depression has been found to have a negative additive effect on cognition (Munoz, 2008). Stewart and colleagues (2011) have reported that cognitive impairment due to depression in ESLD is different to the cognitive impairment in patients with more advance MHE/overt HE has not been thoroughly studied. However the risk of failing to not treat depression in ESLD could lead to clinicians ascribing all cognitive deficits to HE. Stewart and colleagues (2011) focused their study at investigating whether patients with ESLD and depressive symptoms differed from patients with ESLD without depressive

symptoms. The same authors found a significant difference in the domain of working memory of 75 patients at the Mayo Clinic in Rochester, Minnesota. Yet, a recent study conducted in Egypt on 150 patients diagnosed with Hepatitis C did not find a relationship between cognitive functioning and depressive symptoms (Abdel-Mageed, Radwan, Abd El-Bary & El-Desouky, 2015). However, Perrino, Mason, Brown, Spokane and Szaoicnik (2008) found that depression predicts cognitive decline only in adults who have higher levels of education. It is plausible that Abdel-Mageed et al. (2015) could not find an association between cognitive functioning and depressive symptoms owing to the current state of poor education and unqualified teachers in Egypt (Loveluck, 2012).

Anxiety

Additionally, post-traumatic stress and other symptoms of anxiety are common in patients with ESLD and MHE. For instance, Guimaro and colleagues (2011) have reported that 46.2% of their sample of 24 patients presented with high to severe levels of stress and that 33.2% had symptoms of anxiety. According to the DSM 5, post-traumatic stress disorder occurs in the event of an individual being exposed to a stressor (such as death, threatened death, actual or threatened serious injury or sexual violence (see appendix B for post-traumatic stress disorder criteria) (APA, 2013). Furthermore, the criteria specifies that the event is persistently re-experienced whilst there is persistent effortful avoidance of trauma related stimuli resulting in negative alterations in mood, arousal and reactivity. Generalized anxiety disorder is defined as an excessive anxiety and worry occurring more days than not for 6 months. In which, the individual finds it difficult to control the worry and has at least 3 of the following 6 symptoms: restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbances (see appendix C for generalized anxiety disorder criteria). Furthermore, the DSM-5 states neither post-traumatic stress disorder nor generalized anxiety disorder are due to the effect of a substance or alternative psychological

disorder. It is important to note that although patients with ESLD may not be diagnosable with full blown generalized anxiety disorder and/or post-traumatic stress disorder according to the DSM-5 criteria, the patients may show symptoms of the disorder.

Although the current literature search did not uncover documented support for a relationship between anxiety and worsened MHE, previous studies examining the relationship between anxiety and cognitive functioning in other participant cohorts demonstrate impaired performance on tests of processing speed, working memory, inhibition, problem solving, attention as well as immediate and delayed memory (Butters et al., 2011; Richards, Benson, Donnelly & Hadwin, 2014). As such this remains an area that cannot be ignored when considering the functionality of patients with ESLD.

Somatization

International studies have additionally acknowledged the presence of somatization disorder in patients with ESLD (Lopez-Navas et al., 2010). Somatization disorder is a somatoform disorder characterized by a multiplicity of bodily complaints that are very distressing or result in significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings and behaviours regarding those symptoms (see appendix D for criteria) (APA, 2013). However, it is difficult to differentiate between symptoms that arise from immunosuppressant medication, are as a result of ESLD and/or as a result of somatic psychological factors.

Although, the current literature search did not reveal previous studies which examine a possible relationship between somatization disorder and MHE, previous studies have revealed that somatization disorder has a negative effect on cognitive functioning. For instance Trivedi et al. (2005) found that in 22 patients with somatization disorder performed significantly worse on measures of attention, concentration and delayed retrieval than their sex, age and education counterparts. Therefore, if patients with ESLD experience symptoms

of somatization it would be necessary to investigate the association between MHE and somatization.

As can be seen from the above discussion of psychological distress, ESLD and MHE, psychological distress could be associated with a worsened degree of cognitive functioning. It is necessary to recognize the potential psychological distress individuals with ESLD may experience, not only to improve a patient's quality of life but additionally to examine psychological care as a potential treatment opportunity for cognitive dysfunction.

Conclusion

There is a strong argument in the literature that shows that MHE can be a life threatening and debilitating complication of ESLD for the patient. Presently, there is a paucity of both literature and clinical understanding of MHE in patients diagnosed with ESLD in South Africa. As has been noted in the above literature review, left untreated MHE may progress to overt HE which increases the risk of morbidity and mortality. Yet, this phenomenon is poorly understood. While a LT significantly improves the cognitive deficits associated with ESLD, many studies have indicated that there is a probability that not all patients will have complete reversibility of the cognitive deficits. Thus, some patients will experience persistent MHE. It is important to make a contribution to knowledge in this field that can allow for consistent findings as well as to generate changes in clinical practice for patients suffering with ESLD within the South African context (ECAB, 2009). Moreover, it is necessary to recognize the potential psychological distress individuals with ESLD may experience, not only to improve a patient's quality of life but additionally to examine psychological care as a potential treatment opportunity for cognitive dysfunction. Therefore, the current study intends to contribute to the findings by investigating cognitive functioning and psychological distress in patients diagnosed with ESLD in one South African transplant clinic.

Research Questions

Based on the above discussion of the literature relevant to the present study, the four questions guiding the study are as follows:

1) Is the sample of approved patients a representation of the population of patients diagnosed with ESLD at the WDGMC?
2) Is there a significant difference in cognitive functioning for patient's awaiting a LT between initial neuropsychological testing and a 6 month post follow up?
3) Is there a significant difference in cognitive functioning in patient's pre-LT and post-LT?
4) Is there a significant difference between patients who have undergone a LT and those who at the time of testing have not yet undergone a LT?

Chapter 2

Methods

Research Aims

This study intends to examine the evolution of cognitive functioning in patients who have previously been diagnosed with ESLD in (the context of) a South African transplant clinic. Furthermore, the study intends to measure psychological distress in patients who have undergone a successful LT as well as in those patients who have been on the waiting list for a LT for at least 6 months. The aims of the study are:

1. To determine whether the sample of patients selected for a LT are representative of the population of patients with ESLD at the WDGMC?
2. To evaluate changes in cognitive functioning and psychological distress in patients currently on the liver donor waiting list over a minimum of a 6 month period.
3. To assess the role of a liver transplant on cognitive functioning and psychological distress in patients with ESLD.
4. To examine whether there is an alteration in cognitive functioning and psychological distress between liver transplant recipients and liver transplant candidates.

Research Design

The study used a non-experimental, ex-post facto design to investigate changes in cognitive functioning in patients diagnosed with ESLD. As an archival retrospective review of 31 patient's cognitive functioning measured by namely the Repeatable Battery of the Assessment of Neuropsychological Status (RBANS), Stroop Test and Comprehensive Trail-Making Test (CTMT) as well as psychological distress measured by the Brief Symptom Inventory 18 (BSI-18). The analysis was quantitative in nature. Additionally as the patients

cognitive functioning was measured at two points in time, the study is longitudinal (Stangor, 2011). As the study employs an ex-post facto design, it does not allow for experimental causality through the conditions of temporal precedence, co-variation and non-spuriousness. Therefore, it is not possible to draw causal conclusions from the results (Rosenthal & Rosnow, 2008). While this is a typical weakness of a non-experimental design, ex-post facto designs are often the closest that research can come to the nature of the MHE and cognitive impairment, especially within the context of physically ill patients with multiple unquantifiable factors of influence.

Sample and Sampling

During the period of September 2011 to November 2013, 93 patients diagnosed with ESLD completed neuropsychological assessments at the WDGMC (Unpublished Data, WDGMC, 2014). For this study, patients were selected from this population to draw the sample. The patients were divided into two groups based on a criterion of whether they had undergone a LT or not. The transplant group consisted of participants who had undergone an initial psychological assessment and had a successful LT at least 6 months prior to the second point of data collection. The non-transplant group had undergone the initial psychological assessment and were still on the waiting list at the second point of data collection, that is, they had not yet undergone a LT.

Participants were excluded from the study if they had co-morbid DM, overt HE, used alcohol regularly within the last 3 months prior to the interview, had cardiac disease and/or renal failure.

A Non-probability purposive sampling technique was employed to generate the necessary samples. Purposive sampling allows the researcher to choose participants who have a

particular set of criteria, thus insuring that the key constituencies of the study are covered whilst allowing for diversity to be explored (Ritchie, Lewis, & Elam, 2003).

Non-transplant Group

The non-transplant group consisted of 13 participants who were yet to undergo a LT at the WDGMC, however were on the waiting list for a LT and met the aforementioned criteria. The 13 participants included 10 men and 3 women with a mean age of 48.07 years with a standard deviation (SD) of 11.95. The minimum age of the non-transplant participant was 25 and the maximum age was 67. The mean number of years of education was 13 years with a SD of 1.24. The minimum number of years of education for the transplant group was 12 and the maximum was 16. Typically the researcher administered the test to patients whose initial test for LT workup was 13.08 months ago. See Table 2.1 for detailed demographic information of the non-transplant group.

Table 2.1

Demographic variables of the non-transplant group (n=13)

	Frequency	Cumulative Frequency	Cumulative Percentage
Age			
20-29	1	1	7.69%
30-39	2	3	23.08
40-49	3	6	46.15
50-59	5	11	84.62
60-69	2	13	100
Gender			
Male	10	10	76.92
Female	3	13	100
Race			
White	10	10	76.92
Black	2	12	92.31
Indian	1	13	100
Marital Status			
Single	4	4	30.77
Married	6	10	76.92
Divorced	3	13	100
Level of Education			
Matric	7	7	53.85
Certificate	1	8	61.54
Diploma	4	12	92.31
Undergraduate Degree	1	13	100
Postgraduate Degree	0	0	100
Cause of ESLD			
ASH	4	4	30.77
NASH	3	7	53.8
Hepatitis C	0	0	53.8
Hepatitis B	1	8	61.5
PSC	0	0	61.5
Other	5	13	61.5
Months since initial test			
6-8	4	4	30.7
9-11	1	5	38.47
12-14	3	8	61.54
15-17	2	10	76.92
18+	3	13	100

Transplant Group

The transplant group consisted of 18 participants who had undergone a successful LT at the WDGMC and met the aforementioned criteria. The 18 participants included 12 men and 6 women with a mean age of 48.72 years and a SD of 10.98 and ranging from 25-70 years old. The mean number of years of education was 14.28 years with a SD of 2.3. The minimum number of years of education for the transplant group was 11 and the maximum was 20. Typically, the researcher administered the test to patients who had their LT 11.6 months earlier. See Table 2.2 for detailed demographic information of the transplant group.

Table 2.2

Demographic variables of the transplant group (n=18)

	Frequency	Cumulative Frequency	Cumulative Percentage
Age			
20-29	1	1	5.6
30-39	2	3	16.7
40-49	6	9	50
50-59	7	16	88.9
60-79	2	18	100
Gender			
Male	12	12	66.7
Female	6	18	100
Race			
White	12	12	66.7
Black	4	16	88.9
Indian	2	18	100
Marital Status			
Single	4	4	22.2
Married	13	17	94.4
Divorced	1	18	100
Level of Education			
Grade 8-11	2	2	11.1
Matric	4	6	33.3
Certificate	1	7	38.9
Diploma	2	9	50
Undergraduate Degree	3	12	66.7
Postgraduate Degree	6	18	100
Diagnosis			
ASH	2	2	11.1
NASH	3	5	27.8
Hepatitis	4	9	50
PSC	4	13	72.2
Other	5	18	100
Months since Transplant			
6-8	4	4	22.2
9-11	4	8	44.4
12-14	6	14	77.7
15-17	3	17	94.4
18+	1	18	100

Instruments

Questionnaire

The introductory questionnaire contained demographic information (such as age, level of education and marital status) as well as the patients' subjectively perceived levels of cognitive/emotional ability; for instance whether or not the participant had perceived a change in their memory since they had been diagnosed or had a LT. The questionnaire provided the information for the independent variables. Furthermore, participants were also questioned about their experiences of the disease and the complications that occurred. This added depth to the discussion section of the current study. See Appendix E and F for the transplant and non-transplant questionnaire.

Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS is a brief neurocognitive battery which identifies and tracks neurocognitive deficits in a variety of disorders, including ESLD (see Appendix G for the RBANS test content) (Mooney et al., 2007; Randolph, Tierney, Mohr, & Chase, 1998). When used to detect MHE in patients with ESLD the RBANs test encompasses a level of sensitivity superior to that of other cognitive screening measures such as the Psychometric HE Score (PHES) (Mooney et al., 2007). The RBANs test is recommended by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) for use in patients for MHE (Mooney et al., 2007; Randolph et al., 2009). Despite this, given that two of the domains assessed by this battery are of minimal interest to MHE, a modified battery which focuses purely on those cognitive abilities relevant to MHE should be developed (Meyer, Eshelman & Abouljourd, 2006).

The RBANS yields a summary of overall cognitive functioning and examines five cognitive domains comprising of immediate and delayed memory, visuo-construction skills, visuo-

perception, attention and language abilities (Randolph et al., 1998). The test comprises of 12 subsets which are namely list learning, story memory, figure copy, line orientation, picture naming, semantic fluency, digit span, coding, list recall, list recognition, story recall, and figure recall (Randolph et al., 1998). On average the test requires between 20-30 minutes to complete.

Each subset yields a raw score according to the number of correct items given by the patient. Following which the raw score is converted to an index score according to the participant's age in years. For example, for the domain of immediate memory, the raw score for list learning and story memory are added together and converted into an index score and percentile rank according to the participant's age in years. After index scores have been obtained each domain is given a percentile rank. A sum of all index scores provides the total score of neuropsychological status (Randolph et al., 1998).

The RBANS was standardised on a population of 540 North American healthy adult volunteers aged 20-89. The inventory was found to have a strong internal consistency of the total scores which varied from 0.86-.94. However, reliability for the individual subtests is not provided in the test manual. Randolph et al. (1998) reported that split half reliability to be in the 0.80s. Test-retest reliability was evaluated on 40 older adults on the Form A version of the RBANS (pre-test) with an interval of 39 weeks. Reliability coefficients were found to be high on the overall scale (0.88), although they were found to be lower for the individual indices (Randolph et al., 1998).

RBANS scores have been strongly correlated with more extensive assessments such as with the WAIS-R short form test, however the RBANS was found to be more sensitive to impairment than the Weschler tests. The RBANS Manual does not provide factor-analytic data supporting the subscale structure nor does it report how well the subtests comprising

specific indices inter-correlate. Though some evidence of construct validity is reported by the pattern of inter-correlations for the five content indices, with the highest correlation being between the immediate and delayed memory indices (0.63) while the remaining indices are lower and range from 0.28 to 0.41 suggesting relatively different constructs (Randolph, 1998). An additional study led by Gold, Queern, Iannone and Buchanan (1999) found evidence for convergent validity of three of the five indices in the RBANS (immediate memory, attention and delayed memory) using a sample of patients with schizophrenia.

Although an Afrikaans translated version of the RBANS which has considered cultural and linguistic variables for a South Africa population exists, the initial test employed the norms developed for and by Americans. Therefore, the international version was used for the current study. Employing international norms on a multicultural South Africa limits the value of psychological testing due to the complexities and diversity of the population such as age, gender, multiple language differences, cultural differences, varying levels and qualities of education, discrepancies in socioeconomic status as well as rapid acculturation (Foxcroft, 1997; Lucas, 2013; Sehlapelo & Terre Blanche, 1996). Failing to address these essential issues results in a bias. Inferences based on bias are invalid and frequently cannot be generalised across instruments measuring the same underlying trait or ability in other, dissimilar environments (Tanzer, 1997 as cited in Vijver & Tanzer, 2004). These issues will be discussed in further detail later within this chapter.

Stroop Test

The Stroop colour-word test compiled by Golden and Freshwater (2002) measures cognitive flexibility, processing speed and executive function. The Stoop Test is based on the observation that individuals can read words more rapidly than they can identify and name colours. The Golden and Freshwater (2002) standardised version of the Stroop Test uses 3

different colours (green, red and blue) which are presented in block letters and crosses across three 5 by 20 matrices. The three trials include a Word trial (names of colours written in black ink), Colour trial (participant identifies the colour of xxxxx), Colour-word trial (participant reads the name of a colour printed in a different coloured ink, i.e. reads the word red which is printed in blue ink). Scoring for each trial type is based on the number of correct responses in 45 seconds with higher scores indicating a better cognitive performance. The Stoop Test requires approximately 5 minutes to complete (Golden & Freshwater, 2002).

The Stroop Test is highly consistent across different versions of the test (Golden & Freshwater, 2002). Golden (1975) reported high scores of internal consistency for the Golden and Shaw version which were .89, .84 and .73 for the word trial, the colour trial and the colour-word trial respectively. Furthermore, the Stroop Test has construct validity (Chafetz & Matthews, 2004).

Although standardized norms exist for the Stoop Test, the author of the paper employed the international norms as the international norms were used to identify MHE for the pre-test results. As these were not carried out by the author, it was necessary to use international norms. The issues of using a neuropsychological test in a multicultural South African population shall be elucidated later within this chapter.

Comprehensive Trail Making Test

The CTMT consists of a standardised set of five visual search and sequencing tasks that rely on attention, concentration, resistance to distraction and cognitive flexibility. The task of the CTMT is to connect a series of stimuli (numbers, numbers written as words and letters) in a specified order as quickly as possible whilst missing the distractor items. The time taken for the individual to complete the task is recorded in seconds following which the raw score is converted into a T-score and a percentile rank. The test requires approximately 10 minutes to

complete. The CTMT has an internal consistency of α=0.70. Additionally, the test has construct, content and concurrent validity (Reynolds, 2002).

Although standardized norms for the South African population exist for the CTMT, the author of the paper employed the international norms as the international norms were used to identify MHE for the pre-test results. As these were not carried out by the author was obliged to use international norms. See the aforementioned difficulties of using international norms on a multicultural South African population.

Some participants may have performed worse on the CTMT due to extraneous variables which were not controlled for in the initial assessment nor the follow up assessment. These included handedness, arm amputation, deficits in fine motor control and tremors. Handedness causes individual differences cognitive tests. This may be due to a difference in brain symmetry (Prichard, Propper & Christman, 2013). Moreover left handed participants may face problems which right handed participants do not have to consider; for instance whilst writing the left arm may cover the numbers/letters which will subsequently increase the time taken to complete each trial. Another complicating factor, is that patient who have undergone a LT are required to take cyclosporine treatment. Cyclosporine has been found to cause tremors and impaired motor control. Thus, it is probable that this may be a mitigating factor in a test that relies on psychomotor performance (Arria et al., 1991).

BSI-18

The BSI-18 is a psychological self-report symptom scale which was developed from the lengthier instrument, the SCL-90-R. The BSI-18 is a brief measure which takes approximately 4 minutes to administer. The BSI-18 has 18 items which reflects 3 dimensions of psychological distress namely anxiety, depression and somatisation. Each dimension has 6 items which are measured on a 5 point Likert type scale (0-4) ranging from “not at all” to “extremely” with

regards to if the patient experienced the item in the past seven days. To score the BSI-18, each item response is assigned a value from 0-4, following which the values for the 6 item responses are summed which gives a raw score. Subsequently, the raw score is converted to a standardised T-score. The inventory further provides a global score index which is calculated by an addition of the raw scores for each dimension; following which the score is converted to a standardised T-score (Derogatis, 2000).

The BSI-18 has both reliability and validity. Internal consistency was established on a sample of 1134 people. Each dimension produced the following alpha coefficients: somatization α=0.74; depression α=0.84; anxiety α=0.79; total score α=0.89. Additionally, the test has been found to have impressive convergent validity as well as construct validity with little to no disjuncture of items found in a factor analysis (Derogatis, 2000).

Variables affecting neuropsychological test performance

It is incumbent that South African clinicians and researchers alike are aware of the limitations of testing within a multicultural setting as well as the variables that threaten the assumption of equivalence, creating a bias which subsequently could lead to an inaccurate interpretation of the assessment. For the purpose of the paper a fundamental discussion of the variables which may threaten the external validity of a neuropsychological instrument are discussed below.

Gender and age have been linked to altering cognitive ability and consequently test taking performance. Gender differences are not only seen in measures of physical strength but are also apparent in the brain. Based on evidence from fields of neuropsychology, cognition and neuroanatomy, a number of theories have provided support for gender differences in cognitive competence, inter-hemispheric relationships as well as hemispheric specialisations. For example, woman have been found to have superior language abilities to men and men

have been found to have superior mathematical abilities (Doris, O'Neill & Sweetman, 2013; Halpern, 2012). Similarly, aging has been found to impact on neuropsychological test scores. The current work in this area has primarily focused on very old and very young populations due to the exacerbated structural and consequently functional changes in these groups. Generally, increasing age is associated with qualitative changes which can result in more efficient strategies of processing information (Hibbard, Peters, Slovic, Finucane & Tusler, 2001). However, this process plateaus and subsequently decreases with old age. Old age, for example, results in changes to the brains size and vascular structure. Furthermore, communication between neurons decrease as well as a formation of neurofibrillary tangles and senile plaques (Peters, 2006). Accordingly, there is a decrease in memory and speed of processing (Peters, 2006). Thus, age can be shown to have an effect on an individual's test score.

Numerous researchers have pointed to the importance of language in the evaluation procedure within the context a multicultural context as neuropsychological assessments require the participant to understand all test instructions fully. Furthermore, language alters cognitive ability, for instance Palij and Homel (2014) found that bilingualism increases cognitive reserve, improves cognitive flexibility, enhances concentration as well as increases working memory.

Language is additionally dependent on culture and level of acculturation. Acculturation is the extent to which the individual's cultural traditions and practices are retained versus the level of which the individual has acquired mainstream values and standardised norms. Each cultural group is a product of unique physiological and genetic factors that are influenced by familial and social factors which affect development and psychological functioning (Bandura, 1989). Acculturation, therefore, has a moderating effect on test performance as it affects the reliability and validity of a measure as individuals perceive items of an assessment within

cognitive codes based on normative behaviour of their culture (Farmer & Vega, 2010; Bandura, 1989).

Socio-economic status (SES) and the number of resources an individual has available to them is going to additionally affect one's cognitive ability and their test performance. It has been shown that a higher SES is positively associated with psychological features such as self-directedness, expression of uniqueness, control seeking behaviours and an analytic mode of thought in terms of greater attention to an object, semantic categories and a linear view of change (Na et al., 2010). Furthermore, individuals with a higher SES are more likely to have attended school thus they will be more familiar with test taking procedures. According to Foxcroft (2002), test taking wiseness is not something that many people in Africa will be familiar with. Test wiseness has a significant impact on test performance (Nell, 1997 as cited in Foxcroft, 2002). Therefore, those with a higher SES are more likely to perform superiorly on neuropsychological assessments compared to those with a lower SES.

Quality and level of education is a critical and complex variable to include in multicultural assessment. The level of education has an impact on the ability to read, write, work with numbers as well as higher cognitive functions such as attention and reasoning strategies (Foxcroft, 2004). Those with a lower quality and level of education background will most likely not score as highly as those who have higher education backgrounds (Foxcroft, 2004). Within the South African context neuropsychological professionals need to bear in mind the historical disparities of the provision of education (Foxcroft, 2004). Therefore the quality of education is dissimilar within cultural groups in South Africa as well as within rural areas which have not had access to the same academic opportunities and consequently have not developed as high cognitive skills as those who attended school in urban areas (Foxcroft, 2004). Studies in the United States have found that when adjustments are made for the level and quality of education black-white differences of test performance are reduced (Manly,

Byrd, Touradji & Stern, 2004). Furthermore, education is commonly associated with socio-economic status. Typically individuals with an increased socio-economic status are more likely to have a job. Several studies such as Stern (2012) have found that educational and occupational attainment can increase cognitive reserve which consequently slows aging and could potentially delay the onset of dementia. Additionally, a lack of education may result in the individual being illiterate. Illiteracy can affect cognitive abilities such as processing strategies, processing pathways and functional brain organisation (Howieson, Loring & Horney, 2004). Furthermore, illiterate individuals will not be able to complete tests which involve reading (Howieson et al., 2004). Normative data infrequently includes people of low education and illiterate backgrounds (Howieson et al., 2004)

However, the WDGMC is a privatized hospital which disqualifies discrepancies in socioeconomic status as well as varying levels of education – as all participants were shown to have at least a matric level of education. However, the quality of education was not considered. This is vital to reflect upon due to historical division of race which traditionally advantaged "White Model C" schools in South Africa, however with the dismantling of Apartheid there have been an increasing number of opportunities for non-white individuals to access the well-resourced schools allowing for a substantial variability across and within ethnic groups (Shuttleworth-Edwards, Gaylard & Radloff, 2013). This aspect should be considered and addressed in future research studies.

Procedure

After permission was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical), the author was trained in test administration of the RBANS, CTMT, Stoop test and BSI-18 by Tina Sideris, clinical psyhcologist. The researcher was given access to the patient files at the WDGMC. This included the baseline data for the BSI-18, RBANS,

CTMT and Stoop test was collected by a clinical psychologist attached to the WDGMC as part of the LT intake suitability assessment. Demographic information was similarly recorded during this interview. Possible research participants who are patients at the WDGMC were contacted telephonically to be invited to take part in the study. A suitable time was set with participants who agreed to take part in the study. Subsequently, the participants were emailed a short description of the study, a reminder of the meeting as well as two letters of support for the study from the patient's doctors (See Appendix K and Appendix L).

The interviews took place in the rooms at the Transplant Clinic at WDGMC. The participants are familiar with the Transplant Clinic. During the interview participants were be provided with a written information sheet and asked for a signed informed consent for the use of the data in a research report and the possible publications that may arise from this. Participants received altered participant information sheets founded on the premise of whether or not they have undergone a LT or not (see Appendix M and N). Subsequent to obtaining informed consent, participants were required to answer questions on their general well-being. This was followed by the administration of RBANs, the CTMT, the Stroop test and the BSI. The process of informed consent and completion of the neuropsychological tests took approximately 45-60 minutes to complete.

Following data collection completion, the tests were scored, coded and entered onto excel an excel spreadsheet and the RedCap database. SPSS was used to test the research questions.

Ethical considerations

The research study engaged with a vulnerable participant sample and therefore ethical clearance from the Human Research Ethics Committee (HREC Medical) was obtained prior to the study being conducted.

The rights of the participant were protected in this research study as:

1. The principal of autonomy in ethical research was adhered to as participants were afforded the opportunity to make informed decisions with regard to their participation in the study. The participants were informed of their right to decline to participate or withdraw from the study at any time without reason or prejudice.
2. The research adhered to the principle of confidentiality in that it was ensured that identifying information was not included in subsequent reports and articles. However, identifying information, such as the individuals name and surname were necessary to relate their baseline data to the second trial data. After which, the data was coded and identifying information was not stored by the researcher. However, all patients were made aware that as their results are further going to be stored as follow up data in a password protected database (RedCap data) at the WDGMC. Three people have access to the database at WDGMC, Dr Sideris (a clinical psychologist), a data capturer and a data base administrator, all of whom have signed confidentiality clauses. Identifying information is not recorded onto RedCap as each patient has an identifier code for anonymity. Non-disclosure of coded information, data or other material related to the research will be the primary form of confidentiality and the researcher respects the rights of the participant not to have their information destroyed, discussed or disclosed to any group, persons or institution unless otherwise stated and agreed upon in a formal signed confidentiality agreement
3. The anonymity of the participant to the researcher and the personnel at the hospital could not be ensured as the participants were physically present during the assessments. Participant information was kept anonymous from external personnel through the coding of data related to the participant and the removal of all identifying information from the material and data.

4. The participant was provided with an information sheet that ensured the participant's right to make an informed decision about entering into the research study. The information sheet advised the purpose, expected duration, and procedures included in the research in an understandable language. The signed agreement indicated that the research had been fully explained to the participant and that they fully understood their rights as a participant as written in the information sheet (Appendix M and N).

The study had no impact on the participant's physical health nor should the study impact the patient's psychological well-being; however participants were given the right to counselling. In the occurrence of a patient requiring counselling (due to psychological distress, such as anxiety and/or depression about their diagnosis, their role and/or their quality of life) the patients were referred to Tina Sideris, a clinical psychologist at WDGMC, with whom the participants have an established relationship. This was a minimal occurring situation as the study was not deceptive in nature. However, one participant required counselling subsequently to the interview due to actualization of emotional trauma that the process of the diagnosis of end stage LD and transplant had caused. All participants were given the opportunity to be debriefed on the nature, results and conclusions drawn from the research study and were allowed to ask the researcher questions to obtain appropriate information about the study (Appendix M and N).

The researcher avoided abusing power in that the researcher ensured that all participants were treated fairly and respectfully. The researcher did not show discrimination towards any particular participants based on their gender, race, age and the participant's preference to withdraw from the study before, during or on completion of the research process.

Data Analysis

Subsequent to the completion of the interviews, the data gathered from the interviews were scored. The neuropsychological assessments and tests of psychological distress were scored according to the instructions in the test manuals. A detailed explanation of how tests were scored can be seen in Appendix P. Following which the scores were captured on an excel spreadsheet and uploaded onto the RedCap Database. SPSS was utilised to complete the data analysis in order to test the research questions.

Demographic Variables

The demographic variables were analysed to obtain descriptive statistics about the sample. These will included obtaining means and standard deviations for variables of the sample (demographic, cognitive and psychological).

Research Question 1

Research Question 1 of the study was concerned with examining whether or not patients who had been approved for a LT were a representation of all patients with ESLD at the WDGMC. As there is a known population mean score for each variable measured on which to compare the variables of the sample a one sample t-test was applied. The one sample t-test assumes that the dependent variable was normally distributed around the mean. However, normality was assessed using Kolmogorov-Smirnov and was not found and therefore a Mann Whitney U test was applied.

Research Question 2 and 3

Research question 2 investigated the difference in cognitive functioning in patients who, at the point of testing, were on the waiting list for a LT. Patients were measured as the point of an initial assessment as well as in a follow up assessment which occurred at least 6 months

post LT. Research Question 2 explored the possibility of altered cognitive ability before a LT and at least 6 months after a LT. Thus, the author wished to compare the initial data with the follow up data collected from the neurocognitive inventories (RBANS, CTMT and the Stroop Effect Test) in dependent samples. The data collected from these scales was interval in nature. Although, the sample size was less than 30 in both research questions the assumption of normality was tested using Kolmogorov-Smirnov. As a normal distribution was not found a non-parametric test known as Wilcoxon's signed ranked test was used.

Research Question 4

Research Question 4 examined an alteration between independent samples in the neurocognitive inventories. In comparing the two samples the researcher wishes to control for the pre-test scores of the participants thus an analysis of covariance (Ancova) was the most suitable form of analysis. An Ancova assumes that there will be random independent samples, homogeneity of variance (this was tested using Levene's test of homogeneity of variance), a normal distribution (a Kolmogorov-Smirnov test was run and the groups were found to be normally distributed) and that the data is at least interval scale (this assumption is met as the inventories are Likert type scales) (Huck, 2012).

Effect size will be provided for the test results. Effect size provides the power of the statistical result being found. The power of a statistical test refers to the probability that it will lead to the rejection of a false null hypothesis (Greene, 2000). Thus, the power of a test is the ability to test if the effect actually exists.

These analyses were used to answer the research questions offered by the study. The findings shall be presented in the following chapter.

Chapter 3

Results

The following chapter presents the results section of the statistical procedures that were undertaken to explore the research questions. The statistical program used to execute all calculations was SPSS. Scores from the RBANS, Stroop Test, CTMT and the BSI were calculated and produced an overall interval scaled numerical value which was then used as a measure for each quantitative variable. A 95 % confidence interval was selected thus only probabilities less than 0.05 were considered to be significant.

The analysis provides an understanding of the descriptive statistics of each of the variables for each of the groups. Secondly, it is required that the sample of participants is equivalent to the population of patients at the WDGMC to determine if the study can be generalised to the larger population of patients at the WDGMC. The current study aims to ascertain the role of a LT on cognitive functioning as well as the natural progression of MHE in patients who are yet to undergo a LT. Fourthly, it was required to determine the difference in cognitive functioning between patients who had undergone a LT and those who are yet to undergo the LT. Lastly, the relationship between independent variables and the change in cognitive functioning for both transplant and non-transplant groups will be examined.

Assumptions of Parametric Tests

For the purpose of utilizing parametric techniques for the analysis, it was necessary to ensure that four assumptions were met. Random independent sampling was assumed, while the dependent variables all possessed an interval scale. The normality of the dependent variables was determined using graphical histograms, measures of central tendency and the Kolmogorov-Smirnoff test for normality (see appendix P).Examination of the histograms,

Kolmogorov-Smirnoff test and skewness coefficients suggest that the data is not normally distributed for all variables; although many of the variables are normally distributed.

While a log normal transformation could be applied to the data to create a symmetric bell shaped distribution, Feng and colleagues (2014) state that in some cases applying a log normal transformation can skew the distribution further if the data does not follow a log normal distribution. Furthermore, the majority of skewed variables in the current study were negatively skewed. This requires the addition of a small constant to be added to the data. Adding a constant to the data can result in a Type 1 error as Feng and colleagues (2014) found that the p-value of the test is dependent on what value is added to the data before applying the log-transformation. This results in an arbitrary decision of the researcher about the size of the mean to be used in the analysis. To avoid making such errors a transformation was not applied to the data as the current study focused on examining the broad picture of MHE within the South African context. Therefore, for research questions 1, 2 and 3 non-parametric tests were applied.

Regarding, research question 4, Kolmogorov-Smirnov was rerun on the sample of the last research question as it incorporated 13 patients rather than 18. The sample was found to be normally distributed in all indices except for those of the BSI-18. Therefore, a non-parametric Mann-Whitney U test was applied to compare psychological distress between the two groups and a parametric Ancova was applied to compare measures of cognitive functioning. For a parametric Ancova to be run between the transplant patients and the non-transplant patients whilst controlling for the pre-tests scores a further assumption of homogeneity of variance was required. Homogeneity of variance was determined using Levene's Test. Examination of Levene's Test revealed that there is homogeneity of variance.

Descriptive Statistics

The group means (*M*) and standard deviations (*S*) of the population of patients at the WDGMC, the non-transplant and transplant group scores were calculated for each of the variables of interest and their respective components (summarised in Table 3.1 and 3.2 respectively). For the variables that were missing a data point the mean of the group was imputed for that variable point.

Table 3.1

Table showing descriptive statistics of the population of patients at WDGMC (n=93)

		Mean	SD	Minimum	Maximum	Median
Demo-graphics	Age	50.01	11.26	20	72	52
	Education in Years	12.77	1.58	10	16	12
	Disease Severity	16.46	6.60	4	38	16
RBANS	Total Index	80.66	15.37	40	115	81
	Immediate Memory	86.63	15.58	44	114	85
	Visuospatial construction	82.44	15.61	53	112	84
	Language	90.49	15.03	44	127	92
	Attention	76.57	17.82	40	118	75
	Delayed Memory	88.45	16.07	44	118	94
Stroop Effect Test	T-score	36.08	12.26	3	68	37
	Colour T-score	30.80	12.00	3	52	30
	Colour Word T-score	41.63	9.91	14	62	41
	Interference T-score	47.65	6.50	30	61	47.5
CTMT	Composite T- score	35.83	10.46	17	58	38
	Trail 1 T-score	37.49	10.56	18	61	37
	Trail 2 T-score	38.84	11.11	18	68	38.5
	Trail 3 T-score	38.00	11.29	18	65	39.5
	Trail 4 T-score	37.12	10.94	18	62	39
	Trail 5 T-score	35.17	11.07	18	59	37

As can be seen from table 3.1 above, the average age of a patient diagnosed with ESLD is 50.01 with an average education of 12.77 years. The RBANs data shows that for liver patients that the patients show particularly poor results in the Attention (M=76.57) and Visuospatial Construction (M=79.19) indices compared to the immediate memory (M=86.63), language (M=90.49) and delayed memory (M=88.45) indices. Randolph (1998) listed that the average person should score between 90 and 109 for each of the indices and that scores below this are considered to be below average. Comparatively, the average patients with ESLD at the WDGMC scored below average in every index barring for language. It was expected that patients would have below average scores in attention, visuospatial construction and to some degree immediate memory as well as normal language functioning. However, it was not anticipated that on average patients would on score below the norm for delayed memory.

For the Stroop Test, patients scored lower in the Colour test (M=30.80) than the Word test (M=36.08) and the Colour-Word test (41.63). The standardised norm score for the Golden version Stroop test is 38.23. In comparison patients are scoring lower on the colour and word test but above the norm in the colour-word test.

For the CTMT patients scored lowest in trail 5 (M=35.17). According to Reynolds (2002) the typical person should score between 43 and 57. The average patient with ESLD at the WDGMC scored below average in every trail.

This data was statistically analysed by Petra Gaylard for Dr Tina Sideris of the WDGMC (Unpublished Data WDGMC, 2014).

Table 3.2

Table showing descriptive statistics of the non-transplant patients at WDGMC (n=13)

		Pre Test Scores				Follow up Test Scores			
		Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
RBANs	Total Index	78.62	15.99	52	115	77.77	14.01	54	105
	Immediate Memory	87.31	18.5	49	114	84.61	16.15	60	114
	Visuospatial construction	77.54	14,82	58	109	77.31	18.43	60	109
	Language	81.46	25.92	64	104	85.23	9.35	64	97
	Attention	76.77	18.22	53	112	68.34	17.99	40	97
	Delayed Memory	72.38	32.69	44	110	78.34	22.90	48	118
Stroop Effect	Word T-score	30.00	16.74	7	52	33.00	11.44	15	51
	Colour T-score	27.38	14.32	13	49	31.67	13.37	13	62
	Colour Word T-score	39.31	15.72	23	62	42.41	11.75	24	71
	Interference T-score	42.85	20.45	35	62	42.33	9.7	14	54
CTMT	Trail 1	39.38	8.99	27	58	38.85	12.81	18	54
	Trail 2	41.62	12.03	23	59	39.31	12.37	23	60
	Trail 3	39.31	11.7	21	55	36.92	9.24	25	54
	Trail 4	36.92	12.01	19	61	36.39	9.97	20	56
	Trail 5	34.39	16.28	16	54	33.92	7.97	19	44
	Composite T score	36.85	11.78	20	57	29.23	14.19	21	48
BSI-18	Somatisation		n/a			3.92	2.59	0	8
	Depression		n/a			2.69	3.06	0	10
	Anxiety		n/a			5.9	5.31	0	15
	Global Score		n/a			12.54	8.2	0	25

Table 3.2 provides a breakdown of the mean, SDs, minimum and maximum scores for the transplant patients. The participants who are yet to undergo a LT scored low on the indices of attention (M=76.77), delayed memory (M=72.38), and visuospatial construction (M=77.54) in comparison to indices of immediate memory (M=87.31) and language (M=81.46) for the pre-test RBANs test compared to the computed norm. On average patients scored in the 15th percentile, 30th percentile, 16th percentile, 27th percentile, 19th percentile and 30th

percentile for the constructs of total score, immediate memory, visuospatial construction, language, attention and delayed memory respectively. Thus, providing evidence that South African patients at the WDGMC have cognitive deficits at the point of initial testing. For the initial tests participants scored below average compared to the standardised norm for every index. This was not anticipated as patients with MHE do not typically show a deficit in language skills nor delayed memory. However, it is plausible that this finding is as a result of interpreting the test against American norms as an alternative to South African norms. For the Stroop Effect Test non-LT patients scored lowest on the colour score (M=27.38) in comparison to the word score (M=30.00) and the colour word score (M=39.31). Comparatively, non-transplant patients with ESLD at the WDGMC scored below average in the colour score and the word score yet scored average in terms of the colour word score.

For the CTMT participants scored lowest on Trail 5 (M=34.39) and scored highest on Trail 2 (M=41.62) which is just below the average standardised norm which is between 43 and 57. Highlighting that the patients awaiting a LT were below average in terms of attention, concentration, resistance to distraction and cognitive flexibility. On average, patients scored in the 21st percentile for the CTMT composite score and the Trail 1 score; in the 33rd percentile for Trail 2; the 28th percentile for Trail 3; the 26th percentile for Trail 4 and Trail 5. This highlights a poor level of functioning at the initial point of testing for patients awaiting a LT.

For the follow up tests scores, participants scored lowest on the visuospatial construction (M=77.31), delayed memory (M=78.34) and attention (68.84) index scores. For the initial tests participants scored below average (the standardised norm) for every index which was suggested to be between 90 and 109 (Randolph, 1998). On average patients scored in the 14th percentile, 28th percentile, 16th percentile, 21th percentile, 12th percentile and 30th percentile for the constructs of total score, immediate memory, visuospatial construction, language,

attention and delayed memory respectively. Thus, providing evidence that South African patients at the WDGMC have cognitive deficits

For the Stroop Effect Test patients appear to show a marginal improvement in their scores. However, there appears to be a similarity between the interference scores of the pre-test and the follow up test. This could possibly suggest that patients have decreased processing speed in the initial tests rather than an improvement of a cognitive construct.

The CTMT scores appeared to remain static between the initial test and the follow up tests. Patients continued to perform below average in every trail. This highlights a possible deficit in processing speed, attention, concentration, resistance to distraction and cognitive flexibility. On average, patients scored in the 14^{th} percentile for the CTMT composite score; the 25^{th} percentile for the Trail 1 and Trail 2; the 16^{th} percentile for Trail 3; the 18^{th} percentile for Trail 4 and the 12^{th} percentile for Trail 5. Thus, emphasising a progressively worsening level of functioning whilst awaiting a LT

Table 3.3

Table showing descriptive statistics of the transplant patients at WDGMC (n=18)

		Pre Test Scores				Follow up Test Scores			
		Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
RBANs	Total Index	86	23.3	49	156	82.94	19.78	31	111
	Immediate Memory	91.5	21.98	44	156	88.11	16.88	40	109
	Visuospatial construction	88.94	17.93	44	112	85.11	16.1	60	118
	Language	94.94	11.14	66	112	93.89	11.18	60	104
	Attention	72.11	21.07	40	109	87.17	21.57	46	132
	Delayed Memory	87.61	18.38	43	108	92.39	16.49	48	114
Stroop Effect	Word T-score	37.22	15.74	20	81	46.17	13.23	15	66
	Colour T-score	29.44	14.22	10	57	40.33	15.00	8	60
	Colour Word T-score	40.22	11.1	27	56	51.39	9.53	29	67
	Interference T-score	48.67	6.6	39	59	50.06	11.09	20	77
CTMT	Trail 1	32.83	16.4	20	61	39.94	15.43	25	63
	Trail 2	35.11	15.49	21	56	43.94	16.55	28	76
	Trail 3	35.66	17.09	21	63	41.72	14.47	27	82
	Trail 4	35.77	16.81	18	57	43.33	16.16	27	97
	Trail 5	33.55	15.15	20	59	40.39	13.10	30	82
	Composite T score	33.55	15.75	20	56	40.67	15.04	20	62
BSI-18	Somatisation		n/a			5	3.93	0	13
	Depression		n/a			3.22	3.52	0	12
	Anxiety		n/a			5.22	4.96	0	17
	Global Score		n/a			13.44	9.78	0	35

As can be seen from the table 3.3, transplant patients scored low on the indices of attention (M=72.11) in comparison to indices of immediate memory (M=91.5), visuospatial construction (M=88.94), language (M=94.94) and delayed memory (M=87.61). For the initial tests participants scored below average (the standardised norm) for every index which was suggested to be between 90 and 109 (Randolph, 1998). Comparatively, the transplant patients showed to perform above 70 in all indices. Although, the Attention Index was borderline. For the follow up tests scores, participants scored lowest on global cognitive functioning score

(M=82.94), visuospatial construction (M=85.11) and attention (87.17) index scores. On average patients scored in the 29th percentile, 34th percentile, 38th percentile, 43th percentile, 23th percentile and 35th percentile for the constructs of total score, immediate memory, visuospatial construction, language, attention and delayed memory respectively. Thus, providing evidence that South African patients at the WDGMC have cognitive deficits at the point of initial testing.

For the follow up tests scores, participants scored lowest on the visuospatial construction (M=77.31), delayed memory (M=78.34) and attention (68.84) index scores. For the initial tests participants scored below average (compared to the standardised norm) for every index which was suggested to be between 90 and 109 (Randolph, 1998). On average patients scored in the 14th percentile, 28th percentile, 16th percentile, 21th percentile, 12th percentile and 30th percentile for the constructs of total score, immediate memory, visuospatial construction, language, attention and delayed memory respectively. Thus, providing evidence that South African patients at the WDGMC have cognitive deficits.

For the Stroop Effect Test patients scored lowest on the colour score (M=29.44) in comparison to the word score (M=37.22) and the colour-word score (M=40.22) prior to having a LT. The colour-word score appears to be above average whereas the word score and the colour score are below average. Subsequent to having a successful LT, the participants of the study showed an improvement in all indices of the Stroop Effect. However, given the similarity of the interference scores it is possible that there is an improvement in processing speed rather than in executive functioning.

The scores of the CTMT revealed that prior to surgery participants scored below average on every trail. On average, patients scored in the 21st percentile for the CTMT composite score; the 25th percentile for the Trail 1; 23rd percentile for Trail 2; the 29th percentile for Trail 3 and

Trail 4; and the 22nd percentile for Trail 5. Yet following the surgery, there appears to an improvement in all trails which leads the researcher to suggest that there is an improvement in processing speed rather than a specific cognitive construct such as attention. The average percentage rank patients scored increased in comparison to the average percentage rank scored prior to LT. Patients scored, in the 29th percentile for the CTMT composite score; the 32nd percentile for the Trail 1; 40th percentile for Trail 2; the 36th percentile for Trail 3; 39th percentile rank for trail 4; and the 29th percentile for Trail 5.

Research Question 1

Research Question 1 investigated if the sample of approved patients a representation of the population of patients diagnosed with ESLD at the WDGMC. As the assumption of normality was not met, a non-parametric Mann-Whitney U test was used to compare the known mean against the sample of participants in the study.

Table 3.4

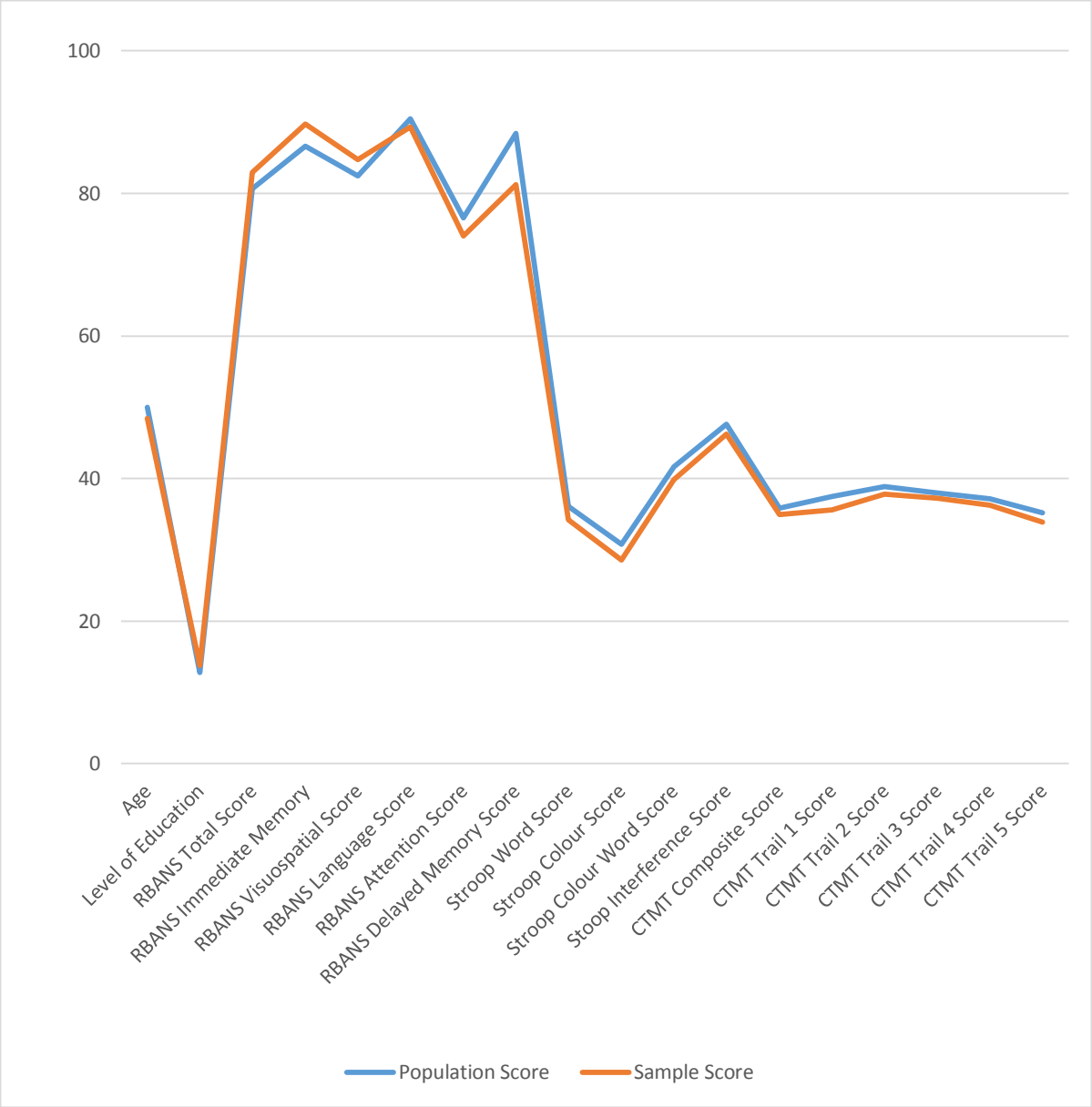
Mann Whitney U Test between population of patients at WDGMC and Sample of participants

	Variable	T Score	Sig (2-tailed)	Effect Size	Effect Size Interpretation
Demo-graphic	Age	-0.749	0.460	0.13	Small
	Education in Years	2.600	0.014*	0.47	Small
RBANS	Total Index	0.607	0.549	0.11	small
	Immediate Memory	0.850	0.402	0.15	small
	Visuospatial/Constructional	0.729	0.472	0.13	small
	Language	-0.341	0.736	-0.06	small
	Attention	-0.706	0.485	-0.13	small
	Delayed Memory	-1.546	0.133	-0.28	Small
Stroop Effect Test	Word T-Score	-0.644	0.524	-0.12	Small
	Colour T-Score	-0.879	0.387	-0.16	Small
	Colour Word T-Score	-0.767	0.449	-0.14	Small
	Interference Score	-0.560	0.580	-0.10	Small
CTMT	Composite Score	-0.353	0.726	-0.06	Small
	Trail 1	-0.760	0.453	-0.14	Small
	Trail 2	-0.390	0.699	-0.07	Small
	Trail 3	-0.300	0.766	-0.05	small
	Trail 4	-0.325	0.747	-0.06	small
	Trail 5	-0.459	0.650	-0.08	Small

*Significant difference in cognitive functioning indicated by * (α=0.05)*

Graph 3.1

Graph showing profile of sample of participants compared to that the population of patients at the WDGMC



Graph 3.1 and table 3.4 represents the sample and population in terms of age, level of education and performance of neuropsychological tests for the initial test conducted. The Mann Whitney U test highlighted that the population of patients and the sample of participants who took part in the study do not significantly differ in terms of cognitive ability

nor age. However, there was a notable difference in level of education. The sample, which includes only patients who have been selected for a LT have a significantly higher level of education than that of the population of patients diagnosed with ESLD. Although, the power of this test is relatively small.

Research Question 2

Research Question 2 examined the whether or not there was a significant difference in cognitive functioning (measured by the RBANS, CTMT and Stroop Effect Test) in patients on the waiting list as it is thought that cognitive functioning should continuously deteriorate as hepatic functioning deteriorates. As a significant difference between two dependent samples is being examined and a non-normal distribution was found a Wilcoxon Sign Rank Test was applied.

As can be seen from table 3.5, a difference was seen in the RBANs Attention Index score, the Stroop effect test scores and all but one of the CTMT trail scores were found to have a significant difference when controlling for the pre-test scores. The RBANs Attention Index score had a significantly lower test score at z=-2.6998 and p=0.007 with a moderate effect size of -0.64.

As previously stated, the Stroop Effect Test scores were also found to be significantly different to the post test scores of the patients awaiting a transplant whilst controlling for the pre-test scores. The Stoop Word T-score was significant at z=-2.724 and p=0.006. The Stroop Colour T-score was significant at the z= -2.920 and p= 0.003. The Stroop Colour Word T-score was found to be significant at z =3.248 and p=0.001. The above indices all had moderate effect sizes.

In addition, patients scored significantly lower in all CTMT trails except for trail 3. Trail 1 was significant at z=-2.306 and p=0.021. Trail 2 was significant at z=-2.786 and p=0.005.

Trail 4 was significant at z=-2.039 and p=0.041. Trail 5 was significant at z=-2.398 and p=0.016. These had moderate effect sizes (except for trail 4 which had a small effect size).

Subsequently, the patients who are yet to undergo a LT performed significantly lower in attention as they scored lower in the follow up tests of the RBANs attention score, the Stroop Effect Test scores and CTMT scores (except trail 3) than their initial test scores.

Table 3.4

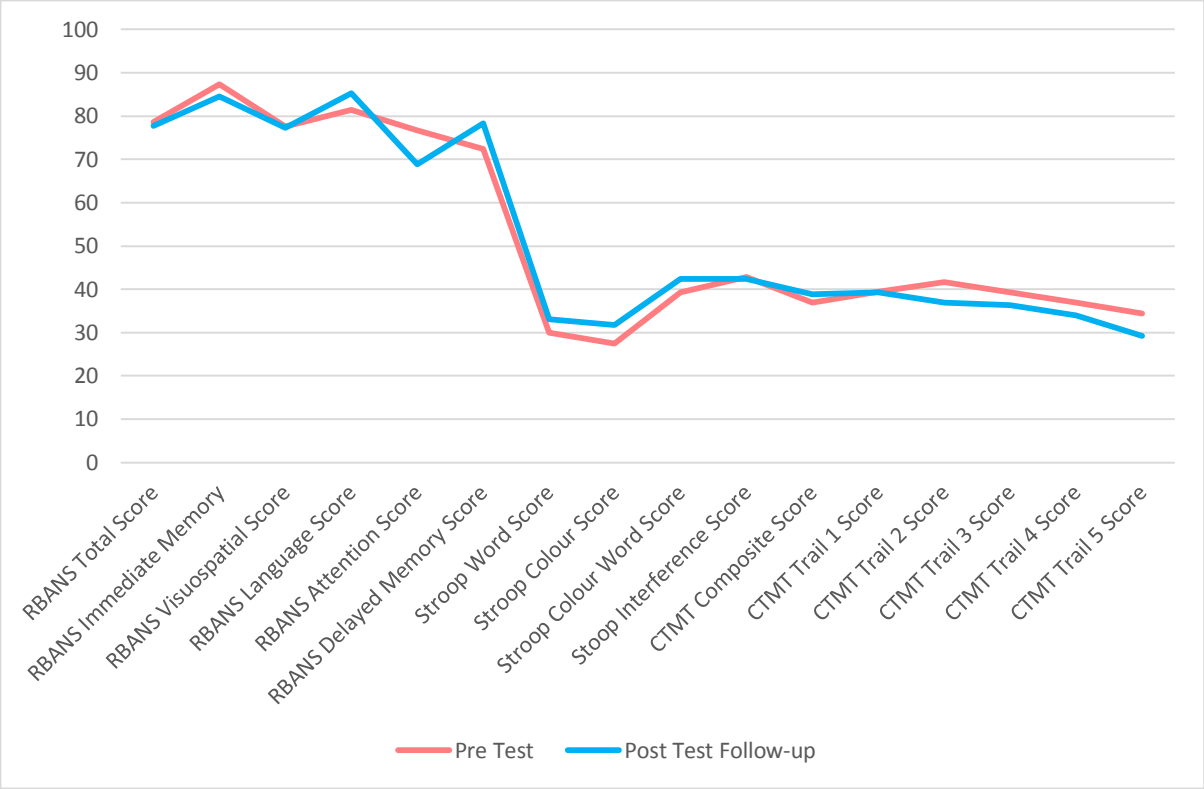
Wilcoxon sign rank test comparing pre-test scores and follow up cognitive profile of patients awaiting for an LT

	Variable	Z Score	Sig (2-tailed)	Effect Size	Effect Size Interpretation
RBANS	Total Index	-0.665	0.506	-0.026	small
	Immediate Memory	-0.769	0.446	-0.18	small
	Visuospatial/Constructional	-1.371	0.170	-0.32	small
	Language	-0.893	0.372	-0.21	small
	Attention	-2.6998	0.007*	-0.64	moderate
	Delayed Memory	-1.852	0.064	-0.44	small
Stroop Effect Test	Word T-Score	-2.724	0.006*	-0.64	moderate
	Colour T-Score	-2.920	0.003*	-0.69	moderate
	Colour Word T-Score	-3.248	0.001*	-0.77	moderate
	Interference Score	-1.099	0.272	-0.3	small
CTMT	Composite Score	-2.533	0.011*	-0.6	moderate
	Trail 1	-2.306	0.021*	-0.54	moderate
	Trail 2	-2.786	0.005*	-0.66	moderate
	Trail 3	-1.824	0.068	-0.43	small
	Trail 4	-2.039	0.041*	-0.48	small
	Trail 5	-2.398	0.016*	-0.57	moderate

*Significant difference in cognitive functioning indicated by * (α=0.05*

Graph 3.2

Graph comparing means of cognitive functioning of the initial test and post-test follow up scores for non-transplant patients



Previous studies have indicated that patients who have MHE are more susceptible to develop overt HE in follow up than patients who do not have MHE. As overt HE can be a fatal complication of ELSD and as the cognitive deficits associated with MHE can have a significant negative effect on daily activities and QoL; it is imperative to understand what, if any factors are related to a worsened cognitive ability.

Therefore, relationships between a change in cognitive functioning and independent variables of length of time since initial test, MELD score (disease severity), cause of ESLD and psychological distress. A change in cognitive functioning was calculated by subtracting the initial score from the follow up score. As a relationship is being examined a non-parametric analysis of Spearman's Rho correlation was applied. The researcher is mindful of the negative impact of data mining on a relatively small sample as it does allow for type 2 errors

(i.e. the chance of not detecting a significant association when one exists to be made which can result in an inaccurate finding.

A relationship was not found for the length of time between the baseline assessment and follow up test and a change in cognitive functioning. This may be due to a static score in LD severity. Table 3.4 showed that there was a relationship between cognitive functioning and the participants MELD score. The MELD score had a strong negative relationship to the Total RBANs Index Score, the RBANS immediate memory score, the visuospatial construction score, the RBANS language score and the RBANS delayed memory score. Therefore, as the MELD score increases (or as ESLD severity increases) the cognitive functioning ability of the patients decreases in the aforementioned areas. As can be seen in table 3.5 an association was seen only for the RBANS test (barring for attention) and not for the Stroop Effects Test or the CTMT. It is not fully understood as to the reasoning for attention, cognitive flexibility, executive functioning and speed of processing are not correlated to disease severity. It is possible that the MELD score does not fully explain the change in cognitive functioning.

Table 3.5

Spearman's Rho Coefficient for Cognitive Ability and severity of ESLD non-Transplant Patients

	Variable	Sig (2 tailed)	r	Strength of Relationship
RBANS	Total Index	0.000*	-0.906	Very strong
	Immediate Memory	0.000*	-0.864	Very strong
	Visuospatial/Constructional	0.003*	-0.758	strong
	Language	0.042*	-0.569	strong
	Attention	0.089	-0.490	No relationship
	Delayed Memory	0.001*	-0.787	Strong
Stroop Effect Test	Word T-Score	0.117	-0.477	No relationship
	Colour T-Score	0.056	-0.565	No relationship
	Colour Word T-Score	0.155	-0.438	No relationship
CTMT	Composite Score	0.714	-0.113	No relationship
	Trail 1	0.809	-0.074	No relationship
	Trail 2	0.442	-0.234	No relationship
	Trail 3	0.640	-0.144	No relationship
	Trail 4	0.404	-0.252	No relationship
	Trail 5	0.730	-0.106	No relationship

*Note Significant correlation between cognitive functioning and MELD score indicated by * ($p<0.05$)*

No relationship was found between any of the post-test cognitive functioning variables and cause of LD for patients currently on the LT waiting list.

A relationship between psychological distress and the change in cognitive functioning was found for patients awaiting a LT. Psychological distress has previously been found to have an

additive negative effect on cognitive functioning. Spearman's Rho test revealed the following associations:

The Somatisation score was found to be correlated to the Total RBANs index score at p=0.26 with a correlation coefficient of -0.612. Therefore, the relationship between somatisation and the Total RBANs index score is moderately negative in strength. As there is an increase in the psychological distress score of somatisation so there is a decrease in overall cognitive functioning. Likewise, a significant association was found for the somatisation score and the RBANS language score (p=0.020). The relationship is moderately negative in strength as the correlation coefficient was -0.634.

The depression score on the BSI-18 was found to be correlated to the RBANs immediate memory, delayed memory and visuospatial construction score. Spearman's Rho revealed a strong negative relationship between immediate memory and depression (p=0.002, r=-0.762). Secondly, a moderately strong relationship was found between visuospatial construction and depression (p=0.033, r=-0.445). Finally, a strong negative relationship was revealed between depression and delated memory (p=0.003, r=-0.750).

It was established that the Anxiety score on the BSI-18 was associated with the RBANs attention and the Stroop effect test scores. The RBANs attention score and anxiety score were found to have a strong negative correlation (p=0.011, r =-0.678). Anxiety was associated with the Stroop word score test as p=0.026 and a correlation coefficient of r=-0.634 which suggests a strong negative relationship. Anxiety was correlated with the stoop colour score at p= 0.41 and r=-0.573 as well with the Stroop colour word score at p=0.012 and r=-0.671.

A correlation was not found for the CTMT scores and psychological distress.

Research Question 3

Research question 3 examined the whether or not there was a significant difference in cognitive functioning (measured by the RBANS, CTMT and Stroop Effect Test) before a LT and after a LT. As a significant difference between two dependent samples is being examined and normality was not found, a Wilcoxon Signed Rank Test was applied.

Overall, it was revealed that there was not sufficient evidence for an improvement in cognitive functioning. This can be seen in Table 3.6 for the RBANs Total Index ($p=0.913$). Residual deficits are found in the domains of visuospatial constructional ($p=0.0170$), as participants were found to score below average in this domain prior to surgery and as well as following surgery. Although a notable improvement was shown in the domain of attention ($p=0.007$), patients who have undergone a LT still score below average in this construct of cognitive functioning. In terms of immediate memory, whilst a significant difference was not found, it is important to note that these individuals did – on average – perform worse in post-test than in the initial test and consequently scored below average. This could be a spurious result.

Through the Stroop Effects Test it can be seen that there is an improvement in the domains of cognitive flexibility, processing speed and executive function at the level of significance of $\alpha=0.05$. As all indices showed a significant improvement.

Through the CTMT results it can be seen that there was a significant improvement in the composite score ($p = 0.011$), Trail 2 ($p=0.021$), Trail 4 ($p=0.041$) and Trail 5 (0.016). Trail 4 and 5 represent divided attention and cognitive flexibility therefore these areas have significantly improved. Trail 1, 2 and 3 represent simple attention. Barring for Trail 3, attention did not show an improvement in the CTMT.

Table 3.6

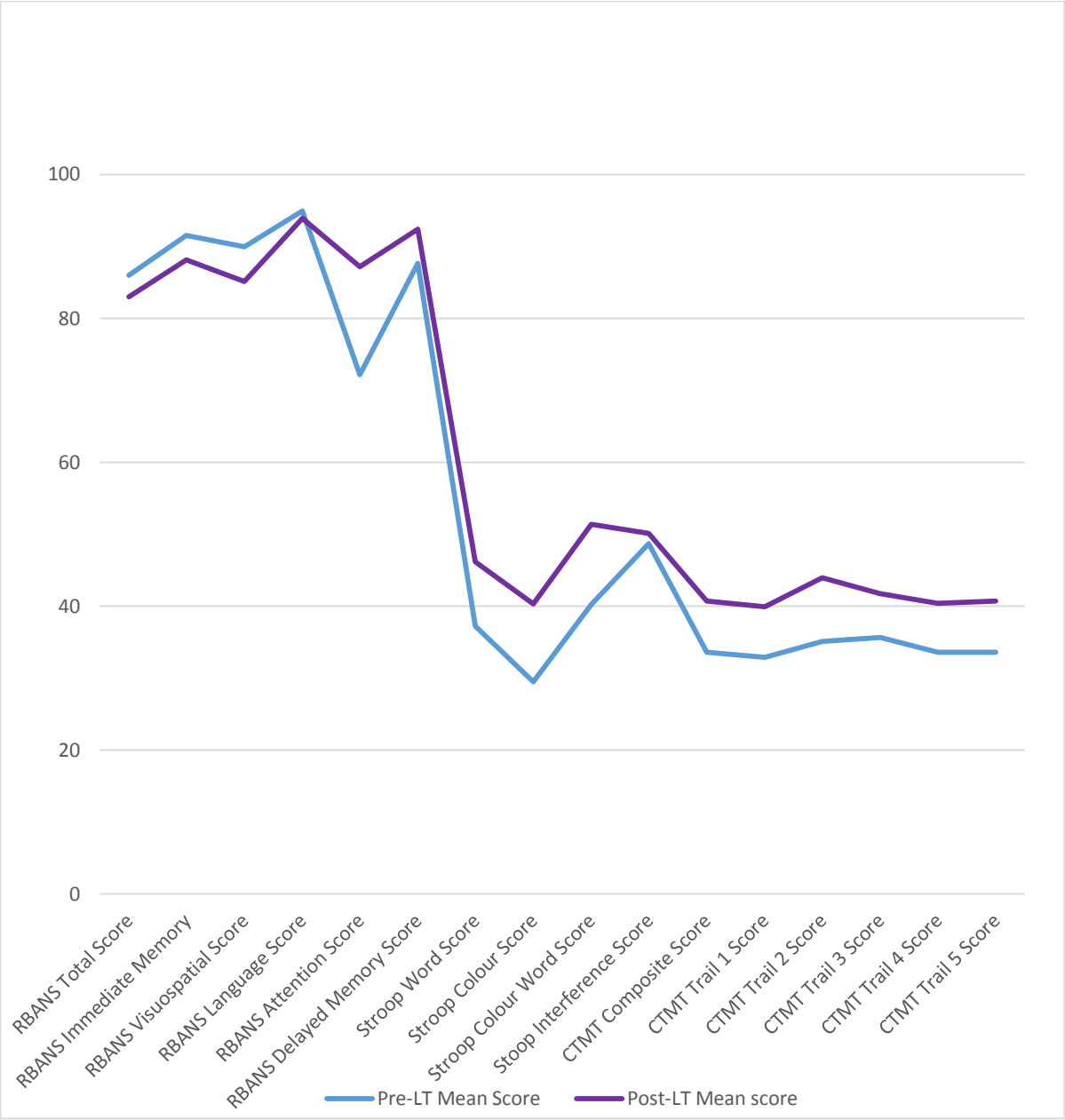
Wilcoxon Signed Rank Test comparing pre-LT cognitive functioning and post LT cognitive functioning

	Variable	Z Score	Sig (2-tailed)	Effect Size	Effect Size Interpretation
RBANS	Total Index	-0.109	0.913	-0.026	small
	Immediate Memory	-0.769	0.446	-0.18	small
	Visuospatial/Constructional	-1.371	0.170	-0.32	small
	Language	-0.893	0.372	-0.21	small
	Attention	-2.6998	0.007*	-0.64	moderate
	Delayed Memory	-1.852	0.064	-0.44	small
Stroop Effect Test	Word T-Score	-2.724	0.006*	-0.64	moderate
	Colour T-Score	-2.920	0.003*	-0.69	moderate
	Colour Word T-Score	-3.248	0.001*	-0.77	moderate
	Interference Score	-2.004	0.037*	-0.40	small
CTMT	Composite Score	-2.533	0.011*	-0.6	moderate
	Trail 1	-2.306	0.021*	-0.54	moderate
	Trail 2	-2.786	0.005*	-0.66	moderate
	Trail 3	-1.824	0.068	-0.43	small
	Trail 4	-2.039	0.041*	-0.48	small
	Trail 5	-2.398	0.016*	-0.57	moderate

*Significant difference in cognitive functioning indicated by * (α=0.05)*

Graph 3.2

Graph showing profile of scores pre LT compared to post LT of transplant patients



To assess the reasoning as to why some patients improve following a LT and other's do not it is imperative to examine the factors which may be associated to cognitive ability for their moderating effect. The independent variables that were investigated for an association with cognitive functioning for the non-transplanted group included length of time since LT, cause of ESLD and psychological distress. As a relationship is being examined a non-parametric analysis of Spearman's Rho correlation was applied. The researcher was mindful of the

negative impact of data mining on a relatively small sample as it does allow for type 2 errors to be made which can result in an inaccurate finding.

As can be seen from table 3.7, a significant association for time in months since the LT and cognitive functioning was revealed. However, an association was only found to occur in the RBANS measure with every item (total index score, immediate memory, visuospatial construction, language, attention and delayed memory) having a strong relationship with length of time, whereby the items showed an improvement since the pre-test. The scores of the CTMT and the Stroop Effect Test were not found to be correlated with the length of time since the patients LT. This may be due to a small sample size, an extraneous variable or a difference in sensitivity of the RBANS test.

Table 3.7

Spearman's Rho Correlation Coefficient for length of time since transplant and cognitive functioning Transplant Patients

	Variable	Sig (2 tailed)	r	Strength of relationship
RBANS	Total Index	0.000*	0.886	Very strong
	Immediate Memory	0.027*	0.530	Strong
	Visuospatial/Constructional	0.030*	0.512	Strong
	Language	0.008*	0.604	Strong
	Attention	0.003*	0.652	Strong
	Delayed Memory	0.020*	0.544	Strong
Stroop Effect Test	Word T-Score	0.530	0.158	No relationship
	Colour T-Score	0.092	0.409	No relationship
	Colour Word T-Score	0.101	0.399	No relationship
CTMT	Composite Score	0.414	0.220	No relationship

*Note Significant correlation between cognitive functioning and length of time by * (p<0)*

Additionally, no relationship was found between any of the post-test cognitive functioning variables and cause of ESLD.

Subsequently, the relationship between psychological distress and the level of cognitive functioning in patients who had undergone a LT was analysed. Psychological distress has previously been found to have an additive negative effect on cognitive functioning. Spearman's Rho test revealed the following associations:

The somatization score was found to be correlated with the RBANS language score (p=0.025) where high levels of somatisation were related to lower scores on the language cognitive functioning index. However, the relationship is only moderately strong (r=-0.402).

The depression score was found to be correlated to both the visuospatial construction score (p=0.032) and the immediate memory score (p=0.012) on the RBANS inventory. It was revealed that the higher the levels of depression the lower the scores on the visuospatial construction score and immediate memory score. Both were found to have a strong association with depression (visuospatial r=-0.506; immediate memory r= - 0.576). Furthermore, depression was found to be correlated to the Stroop Effect Test scores as well as the composite CTMT score. The Stroop Effect Test significance values were as follows: Stoop word score p=0.024; Stroop colour score p=0.029; and Stroop colour word score p=0.044. The CTMT composite score was significantly correlated to depression at p=0.004. It was revealed that the aforementioned scores decreased as there was an increase in depression. The correlation coefficients were as follows; Stroop word score r=-0.528 (strong negative relationship); Stoop colour score r=-0.513 (Strong negative relationship); Stroop colour word score r=-0.480 (moderately strong negative relationship) and the CTMT composite score r=-0.646 (strong relationship).

The Anxiety score was found to be correlated to both the attention score from RBANS (p=0.005) as well as the CTMT composite score (p=0.040). Therefore, anxiety was found to be correlated with complex attention as well as simple attention. It was revealed that the higher the levels of anxiety the lower the scores on the attention scores. The RBANS attention score had a strong negative relationship with anxiety (r=-0.631) and the CTMT composite score had a moderate negative relationship with anxiety (-0.428).

Research Question 4

Research Question 4 investigated whether a significant difference existed between patients who have undergone a LT and those who at the time of testing have not yet undergone a LT. In comparing the two samples the researcher wished to control for the pre-test scores of the participants and thus an analysis of covariance (Ancova) was the most suitable form of analysis.

For Question 4, all non-transplant patients were used, whereas 13 participants from the transplant group were made use of which were as similar to age (not more than a 5 year difference) as well as the same gender as the non-transplant group were used to run the Ancova.

As can be seen from table 3.7 only the RBANs Attention Index score and the Stroop effect test scores were found to have a significant difference when controlling for the pre-test scores. The RBANs Attention Index score was significant at f=5.764 and p=0.025. The post test scores of the transplant patients showed a significantly large improvement compared to the post test scores of the patients awaiting a transplant.

As previously stated, the Stroop Effect Test scores of the patients who has undergone a LT were also found to be significantly different to the post test scores of the patients awaiting a transplant whilst controlling for the pre-test scores. The Stoop Word T-score was significant at f=12.838 and p=0.002. The Stroop Colour T-score was significant at the f = 4.016 and p= 0.014. The Stroop Colour Word T-score was found to be significant at f=5.101 p=0.034. Subsequently, the patients who had undergone an LT performed significantly better to the patients who are still awaiting an LT on the Stroop Effect Test.

Table 3.8

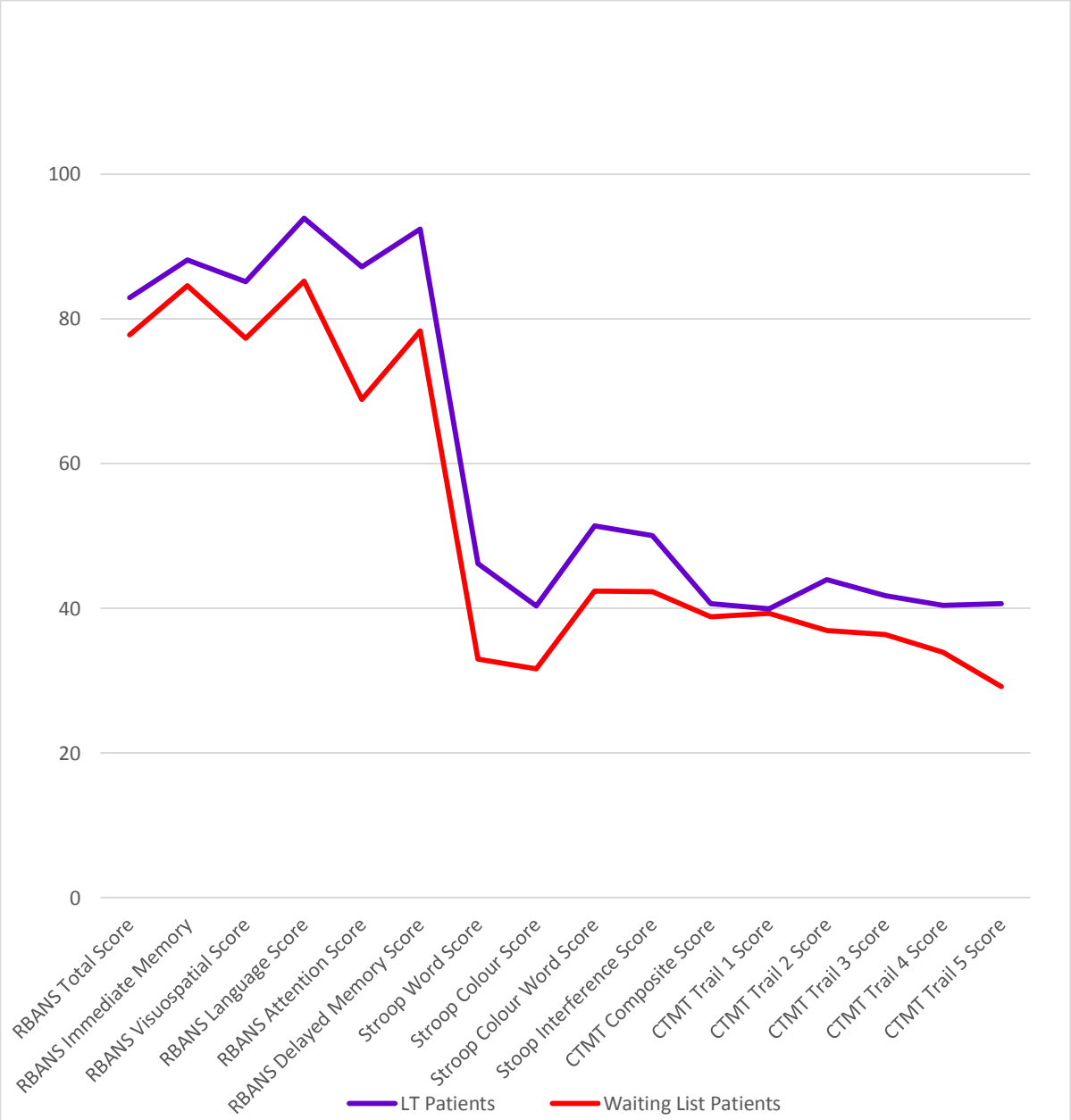
Ancova Test Controlling for pre-test scores and Cognitive Ability Transplant and non-transplant group

	Variable	F Score	Sig (2-tailed)	Effect Size	Effect size interpretation
RBANS	Total Index	0.010	0.921	0.000	Small
	Immediate Memory	0.113	0.740	0.005	Small
	Visuospatial/Constructional	0.046	0.831	0.138	Moderate
	Language	3.851	0.062	0.143	Moderate
	Attention	5.764	0.025*	0.200	Large
	Delayed Memory	2.412	0.134	0.095	Moderate
Stroop Effect Test	Word T-Score	12.838	0.002*	0.369	Large
	Colour T-Score	4.016	0.014*	0.154	Large
	Colour Word T-Score	5.101	0.034*	0.188	Large
	Interference Score	3.280	0.048*	0.130	Moderate
CTMT	Composite Score	6.153	0.021*	0.211	Large
	Trail 1	1.782	0.195	0.072	Moderate
	Trail 2	4.006	0.057	0.148	Moderate
	Trail 3	2.557	0.123	0.100	Moderate
	Trail 4	3.118	0.091	0.119	Large
	Trail 5	7.503	0.012*	0.246	Large

*Significant difference in cognitive functioning indicated by * (α=0.05)*

Graph 3.4

Graph comparing differences between LT patients follow up and patients on the waiting list follow up



Additionally, an alteration in psychological distress between the patients awaiting a LT and patients who have undergone a successful LT was applied and the two samples were compared. However, as there were no pre-test scores recorded and therefore the pre-test scores could not be controlled for; patients in the transplant group were matched to patients in the non-transplant group according to demographic information (age, race, gender, level of

education and diagnosis and RBANS total index score) to control for differences in scores. Due to a lack of homogeneity of variance and normality a non-parametric Mann-Whitney U test was applied.

As can be seen from table 3.12 a significant difference in psychological distress was not revealed between the patients awaiting a LT and those who had previously undergone a LT

Table 3.9

Mann-Whitney U Scores for BSI-18 Non-Transplant Patients

	Z-Score	**Sig (2-tailed)**	**Effect Size**	**Effect Size interpretation**
BSI-18 Somatisation	-0.594	0.552	-0.369	Small
BSI-18 Depression	-0.310	0.757	-0.266	Small
BSI-18 Anxiety	-0.077	0.938	-0.133	Small
BSI-18 Global	-0.644	0.520	0.385	Small

*Note Significant difference in psychological distress indicated by * ($p<0.05$)*

This chapter has presented the statistical analyses employed to answer the research questions. In summation, the results of the various composite scales of the different measures could potentially provide insight into the nature and processes of MHE in patients diagnosed with ESLD in South Africa.

Chapter 4

Discussion

Introduction

MHE is a frequent complication of ESLD affecting 30-80% of those diagnosed with ESLD. Although research efforts over the last decades have greatly expanded the knowledge in MHE, few studies have focused on the reversibility of MHE following a LT. Furthermore, studies which have focused on the reversibility of MHE have found contradictory results. Several studies have revealed that patients have had a full reversal of the cognitive deficits associated with MHE (Cordoba et al., 2001; Naegele et al., 2000). Other more recent studies have argued that even though there is an improvement in patient's cognitive performance on neuropsychological tests the patients' did not fully recover their cognitive functioning (Mechtcheriakov et al., 2004; O'Carroll et al, 2003). Furthermore, there has been a lack of studies which measure the natural progression of MHE whilst a patient is awaiting a LT. Additionally, these studies have not been conducted within a South African context neither have they examined the relationship between the cause of ESLD, severity of ESLD, length of time since LT, psychological distress and the change in cognitive functioning.

Representation of Sample

The participants of the study were compared to the population of patients at the WDGMC with ESLD. This was done to ensure that a generalisation could be made from the sample of participants to the population of patients. The participants of the study who would have to have been approved by a panel of multidisciplinary specialists were a representation of the population of patients, which included both approved patients and patients who were not selected to undergo a LT. The panel involves a multidisciplinary team who determine the severity of the disease, exclude contra-indications, optimize pre-transplant care and candidate

condition, educate the patient and family on post procedure implications and ensure that psychosocial circumstances support post-transplant treatment and lifestyle requirements (Zuckermann & Loveland, 2012). In addition at the WDGMC the psychological assessment includes an assessment of cognitive functioning.

The current study, applied a Mann-Whitney U test to determine whether the sample of patients significantly differed in age, years of education, RBANS score, Stoop effect test scores and CTMT scores to the population of patients at the WDGMC. It was found that the sample of patients did not significantly differ on any of the factors except for the number of years of education. This is an unexpected result as level of education has been revealed to have an effect on neuropsychological test performance, yet the sample of patients did not show enhanced scores in any of the neuropsychological tests (Ardila, 1996; Ardila et al., 2000; Hooren et al., 2007; Strauss, Sherman, & Spreen, 2006).

Education increases cognitive reserve. According to Stern (2002) cognitive reserve can be defined according to two models; active or a passive term. In passive models, reserve is defined in terms of the amount of damage that can be sustained before reaching a threshold for clinical expression (Stern, 2002). Brain reserve, first described by Katzman (1993) is an example of a passive model, where reserve derives from brain size and therefore larger brains can sustain a higher level of injury before a clinical deficit becomes clinically present. This approach to reserve has been categorised in the threshold model first described by Satz (1993). The threshold model recognizes that there are individual differences in brain reserve capacity. Furthermore, it assumes that once brain reserve capacity is depleted past some fixed critical threshold, specific clinical or functional deficits emerge (Stern, 2002). Contrastingly, active models of cognitive reserve revolve around differences in how the task is processed (Stern, 2002). Active models of cognitive reserve propose that the brain actively attempts to

cope with brain damage by using pre-existing cognitive processes or by relying on compensatory processes (Stern, 2002).

Patel et al. (2014) noted that the effect of MHE and ESLD is determined by cognitive reserve. This was determined in their study of 118 patients without overt HE whereby patients who performed abnormally on 2 pencil and paper neuropsychological batteries were considered to have MHE. Patients who had MHE had significantly lower levels of cognitive reserve in comparison to patients without MHE irrespective of ESLD disease severity. Therefore, as education increases cognitive reserve it is likely that patients with higher levels and quality of education will have higher levels of cognitive reserve resulting in superior performance on neuropsychological tests.

Education further increases the strength of skills necessary to complete neuropsychological tests. Richardson and Marottoli (1996) demonstrated this effect by providing normative data adjusted for level of education and showed that the performance of older individuals on a variety of common neuropsychological tests was worse when they had less than 12 years of education as opposed to more than 12 years of education. Additionally, Hooren et al. (2007) showed that individuals with a middle (estimated by intermediate secondary and intermediate vocational education) or high (estimated by any higher tertiary/secondary/vocational education) level of education outperformed individuals with a low level of education (estimated by elementary/lower vocational education) on a variety of neuropsychological tests.

It is plausible that other factors which affect neuropsychological test performance are moderating the relationship between the sample of participants and the population of patients. For instance, it would be reasonable to postulate that even though the sample of participants have significantly more years of education than the population of participants the quality of

education is similar. Nell (2000) asserted that an individual with 12 years of education at an under-resourced school cannot be compared to an individual with the same number of years of education from a well-resourced school. This is especially true in the South African context, due to the legacy of apartheid as well as vast demographic differences in terms of opportunities, resources and facilities. (Skuy, Schutte, Fridjhon & O'Carroll, 2001). As this was not measured in the study it cannot be elucidated if this is a plausible hypothesis.

Likewise, the sample of participants may have had a significantly worse ESLD severity (measured by the MELD score). Some researchers have found a correlation for the MELD score and neurocognitive test performance. As the MELD score was not compared between the two groups it cannot be clarified that the sample of participants had more severe ESLD which resulted in a decreased performance on the neuropsychological tests. Additionally, due to the small effect size (d=0.97), it is possible that it is a completely spurious result caused by a type II error.

It can be seen that the WDGMC does not discriminate that patients with MHE should receive a LT sooner than patients without MHE. This is in accordance with international standards which suggest that a liver organ allocation is prioritised according to three categories, namely medical urgency, utility and transplant benefit (Cholongitas & Burroughs, 2012). Yet, the current standard does not consider bouts of HE nor MHE to play an integral role in the aforementioned categories even though MHE is considered by some to significantly increase the possibility of morbidity and quality of life (Wakim-Fleming, 2011). Therefore, it may be in a patient's best interest, and therefore a gold standard of practice to include cognitive functioning as a determining factor for prioritisation of patients on the waiting list for a LT. This has further been recommended by the American Association for the Study of Liver Disease (Wakim-Fleming, 2011).

MHE in South Africa: Baseline Scores

Patients diagnosed with liver disease, undergo a comprehensive pre-transplantation evaluation which includes a patient's medical history, liver function tests, blood tests (this is used to assess whether the liver creates proteins which clot blood and for levels of immunology), and pulmonary function tests, to name but a few (Koffron & Stein, 2008). In addition to the above-mentioned medical profiling, internationally, the standard protocol for many institutions includes psychological and neuropsychological evaluation of the patient. Despite the fact that neuropsychological assessment is the only method of detecting MHE, the vast majority of hospitals in South Africa do not presently include this as part of their evaluation, barring for the WDGMC (Amodio et al., 2008). Additionally, prior to the present study, no previous studies had eluded to and therefore provided evidence for MHE within the South African context. The current study investigated this internationally commonly found complication of ESLD in a cohort of 18 transplanted patients and 13 patients who at the time of testing were on the waiting list for a LT.

For the baseline test, it was found that 48.39% of the participants in the study showed at least one cognitive deficit on the RBANs when compared to 2 SDs below the standardised norm score. This is in accordance with the prevalence of MHE in international settings, which document that between 30-80% of patients have co-morbid MHE (Dhiman & Chawla, 2009; Liu et al., 2004). This corroborates preliminary data of MHE in South Africa which suggests that 40-50% of patients have cognitive deficits associated with MHE (Sideris, 2014).

In agreement with previous studies the baseline data showed that participants typically scored just above average in measures of attention, visuospatial construction, cognitive flexibility and speed of processing (Meyer, Eshelman & Abouljoud, 2006, Randolph et al., 2009). Interestingly, the non-transplant participants showed an almost below the standardised norm

score in delayed memory - a fairly uncommon finding. Diminished scores in memory are often a consequence of inefficient cognitive processing speed
(McCrea, Cordoba, Vessey, Blei & Randolph, 1996; Weissenborn et al., 2003).

Natural Progression of MHE

Patients who are on the waiting list for a LT may, in terms of MHE, in some cases improve or remain unchanged over a long-term follow-up. However, characteristically, patients with ESLD deteriorate and develop overt HE. The development of overt HE is commonly precipitated by gastrointestinal bleeding, medications (anti-depressants and benzodiazepines), constipation, diuretic therapy and/or dietary protein overload (Jones, 1997). However, it has been found that MHE predicts the probability of an individual developing overt HE (Dhiman & Chawla, 2009; Romero-Gomez et al., 2001).

The results of a non-parametric Wilcoxon Sign Rank Test revealed selective decreases in cognitive functioning. That is to say that significant differences in cognitive functioning between the initial test and the follow-up were not consistently found. The sample of 13 patients awaiting a LT did not show a change in immediate memory, visuospatial construction, language and delayed memory. In contrast, measures of attention, concentration, executive functioning, cognitive flexibility, processing speed were notably lower at the follow up test in comparison to the initial assessment. The cognitive domains which patients awaiting a LT performed worse in shall be examined, these include attention and processing speed.

Attention is not a single entity. Rather, attention is a finite set of brain processes that interact mutually with other cognitive processes, such as selection, vigilance and control (Parasuraman, 2000). Each sensory modality has an attentional system (for instance there is visual attention, olfactory attention, auditory attention, tactile attention and gustatory

attention) (Parasuraman, 2000). Disturbances of the mechanisms of attention may affect the performance of other cognitive domains. Reduced attention skills strongly correlate with specific domains of cognitive function, such as memory, decision making and higher visual functioning as well as overall cognitive ability.

The present study found that patients showed progressively lower scores of processing speed as seen in the CTMT and the Stroop effect tests. Processing speed is a basic cognitive or brain process that is apparent in many higher-order cognitive domains, such attention and executive functioning. Therefore, as most of the tasks that assessed attention were dependent on processing speed it could be argued that it is not necessarily attention that is the main pathological deficit of MHE. Reasonably, it could be speed of processing and motor dysfunction that are the chief pathological deficits of MHE.

Masterson and O'Carroll (1995) reported that the most common cognitive domain in patients with varying degrees of HE is that of psychomotor slowing. O'Carroll and colleagues (2003), used cognitive assessments as well as single photon emission computerised tomography to compare patients with cirrhosis to healthy matched controls. They found that the cirrhotic group were significantly impaired in psychomotor slowing. The single photon emission computerised tomography results of the same study identified bilateral hyper-metabolism in the basal ganglia in patients with cirrhosis. The basal ganglia, which, through MRI studies has been shown to have manganese levels seven times higher than normal, has been correlated to speed of processing (Batista et al., 2012; Butterworth, Spahr, Fontaine & Layrargues, 1995).

As attention is dependent on processing speed additional studies need to focus on identifying whether neuropsychological tests represent a deficit in speed of processing rather than attention or vice versa.

Ideally, patients should be tested every six months to 1 year after the initial test so as to measure the trajectory of MHE in patients as well as manage worsened cognitive functioning. This will allow for a pattern to be established for worsened cognitive functioning in patients. This should be done not only for research purposes but additionally within clinical settings so that additional treatment may be given to patients who have increasingly worsened cognitive functioning. Attention is an aspect of cognitive functioning which has been found to significantly decrease for patients with MHE within South Africa and is used in everyday tasks such as driving a car. Previous studies of driving ability using on-road driving tests have demonstrated that MHE patients have significant defects in reaction time, resulting in their assertion as unsafe drivers (Bajaj et al, 2008; Wein et al., 2004). Thus, the clinical setting should carefully monitor patients operating heavy machinery so as to ensure their safety as well as the safety of others.

Factors associated with the progression of MHE

Previous studies have indicated that patients who have MHE are more susceptible to develop overt HE in follow up tests than patients who do not have MHE initially. As overt HE can be a fatal complication of ELSD and as the cognitive deficits associated with MHE can have a significant negative effect on daily activities and quality of life it is imperative to understand which, if any factors are related to a worsened cognitive ability. The factors examined were the length of time since the baseline test, disease severity, cause of ESLD and psychological distress.

No relationship was found between length of time from the baseline test and the follow up battery of cognitive functioning tests. This may be due to a static score in ESLD severity. The correlation between ESLD severity, represented by the MELD score, found an association between the change of cognition of immediate memory, the visuospatial construction score and the RBANS language score as well as the RBANS delayed memory

score and length of time. This was an unexpected finding as a significant change in cognitive functioning was not demonstrated through these scores. Previous studies have highlighted strong correlations for the MELD score and all areas of cognitive functioning (Meyer et al., 2006; Sorrell et al., 2006). It is important to establish whether the MELD score is related to cognitive functioning as studies which ignore the plausible relationship could distort results.

No association was found between the cause of ESLD and a difference in cognitive functioning. Patients diagnosed with ASH have previously been found to exhibit more severe deficits in episodic memory, working memory, executive functions, visuospatial construction abilities and motor deficits than patients with diagnosed without ASH (Dawson & Grant, 2000; Pitel et al., 2007; Sullivan, Rosenbloom, & Pfefferbaum, 2000). Such a study is also reported by Sorrell, et al. (2006) where patients with ASH ESLD scored significantly lower on the RBANS than patients with other causes of ESLD. In the same study, patients with cholestatic ESLD performed better in the RBANs compared to those with ASH. Therefore, the authors concluded that it is plausible that cognitive dysfunction is more severe in patients with ASH. It remains unclear as to whether the disturbance of brain function in patients with ASH is as a result of MHE or alcohol toxicity (Vilstrup et al., 2014). Likewise, increasing evidence exists that patients with Hepatitis C suffer from chronic fatigue, verbal learning, attention, executive functioning and memory deficits regardless of the severity of the liver disease (Forton et al., 2002; Poynard et al., 2002; Weissenborn et al., 2004). As a relationship was not found for aetiology and cognitive functioning it suggests that hepatic dysfunction is the over-riding contributor to cognitive dysfunction (Pantiaga et al., 2003).

An association was found between psychological distress and cognitive functioning. Somatisation was found to be associated with the Total RBANs Score. This is the first study known to the author that has examined somatization and cognitive functioning in relation to patients with ESLD Previous studies have revealed that somatization disorder has a negative

effect on cognitive functioning (Trivedi et al., 2005). Hall, Kuzminskyte, Pederson, Ombol and Fink (2011) noted that patients with somatization have cognitive deficits in attention and processing speed whereas a study conducted by Niemi, Portin, Aalto, Hakala & Karlson (2002) found that individuals with somatization symptoms performed lower on tests of verbal ability, memory and attention. Trivedi et al. (2005) found that their cohort of participants performed worse in measures of attention, concentration and delayed retrieval than their sex, age and education equivalent counterparts. The multiple findings therefore may highlight that somatization affects many areas of cognitive functioning rather than a specified locale.

However, somatization for patients with a medical condition such as ESLD could be caused by various plausible alternatives which are not psychological but are rather a reality of living with a serious illness and therefore are faced with an acute stress reaction which increases cognitive load (Hall et al., 2011). Additionally Patients with ESLD experience pain and fatigue (Boyd, Kimbell, Murray & Iredale, 2012). Both pain and fatigue have been found to be related to cognitive functioning and therefore may be further contributing to the current findings. Pain has previously been found to be associated with impairments in attention, learning, memory, speed of information processing, psychomotor ability and executive functioning (Moriarty, McGuire & Finn, 2011). While, fatigue has been found to be related to impairments in attention, concentration and memory performances (Neu, Kajosch, Peigneux, Linkowski & Le Bon, 2011).

Depression was found to be related to memory and visuospatial construction. Several studies, both internationally and within the context of South Africa highlight the relationship between memory and depression. A meta-analytic review of 99 previous studies investigated the associations between memory impairment and depression and revealed a significant, stable association between depression and memory impairment (Burt, Zembar & Niedereche, 1995). Therefore, this pattern is not uncommon and is expected in a cohort of ESLD patients.

Furthermore, the relationship between visuospatial construction scores and depression were also expected as previous international studies on other patient cohorts have also found this relationship (such as Bhalla et al., 2006).

Anxiety was found to be related to the scores of attention (both Stroop Effect Tests scores as well as the RBANs attention score). Anxiety is characterised by a lack of control which has led to the hypothesis that anxiety modulates attention; whereby as anxiety increases the threat value assigned to a situation which gives rise to a tendency to constantly direct attention towards the source of threat. Using the Posner Model of attention described in the literature review, anxiety specifically has been found to affect alerting and orientating attentional networks.

The Role of an LT on cognitive functioning

The role of a LT on cognitive functioning was established in an earlier study which examined patients with cirrhosis who underwent an assessment of neuropsychological functioning following episodes of overt HE. The study revealed that patients who had experienced episodes of overt HE performed worse on neuropsychological tests after a LT than control subjects, even though the patients with overt HE showed an improvement. This established that HE has a metabolic component that improves with reversal of liver failure and a structural component which persists regardless of the improvement of liver failure (Bajaj et al., 2010).

Alterations in MHE in response to liver transplantation (LT) should be taken into account as residual cognitive deficits, such as visuo-motor slowing and attention deficits, may significantly influence the everyday functioning of post LT patients and reduce the general clinical and psycho-social benefit of a LT (Mechtcheriakov, et al., 2004). The importance of the issue of reversibility of MHE escalates due to the constantly increasing waiting time for a

LT and due to the current lack of a neuro-protective treatment for patients with cerebral deficits and ESLD (Mechtcheriakov et al., 2004).

The long term effect of a LT on cognitive functioning and the reversibility of MHE has been well documented internationally. However, the studies produced contrasting results and therefore, it was impossible to transpose previous international literature with inconsistent findings to predict the outlook of cognitive functioning in patients in South Africa who have undergone a successful LT. Several international studies have documented a substantial improvement in cognitive functioning post LT, such as Weissenborn and colleagues (2003) as well as Cordoba and colleagues (2001).

The current study implemented three neurocognitive tests to examine cognitive performance in a sample of 18 participants from the WDGMC. The neurocognitive tests were the RBANs, the CTMT and the Stroop Effect Test. The tests were conducted at two points in time. Firstly, at the initial point of testing patients underwent neurocognitive testing as part of their work up for a LT at the WDGMC. The second point of testing was conducted at least 6 months subsequent to the participant having undergone a successful LT.

The present study revealed a significant improvement in attention as well as in delayed memory. This is in accordance with many previous studies which focused on the role of a LT on cognitive functioning and found a substantial improvement. Naegele and colleagues (2000) revealed in a study of 8 participants who were seen 3-7 months post-LT, had no residual signs of MHE. Hockerstedt et al. (1992) reported similar findings in that the majority of neurological impairment of 8 patients diagnosed with ESLD ceased 6-12 months post LT. Lazeyras et al. (2002) observed a normalisation of spectroscopic changes in patients after a LT who had previously been diagnosed with MHE. O'Carroll et al. (2003) performed a large prospective study over a 3-year period in which neuropsychological data were prospectively

collected from 164 patients who were assessed for LT. One-year post-LT, follow-up data from transplant recipients showed significant improvement in most psychological domains. Cordoba and colleagues (2003) ran an MRI test in patients with ESLD and found a high signal intensity in the basal ganglia ad the corticospinal tract. The authors found that both of these abnormalities substantially improved 1 year following a successful LT. Furthermore, Garcia-Martinez et al. (2011) indicated that a LT is able to significantly improve a patients cognitive functioning despite the risk of surgery, the neurotoxicity of immunosuppressant therapy, the effect of aging and other related comorbidities.

However, as previously stated the finding for a complete reversal in MHE have been inconsistent with many of the studies finding that there are residual cognitive deficits. The study revealed that a deficit remains in visuospatial construction. This is in accordance with Mattarozzi et al.'s (2004) study of 62 patients before and after LT. In that patients presented with persistent cognitive deficits of visuospatial construction 6-18 months post operatively. Mattarozzi et al. (2004) additionally found an improvement in attention tasks in the same group of participants. Neuroimaging studies have revealed similar results of patients with cirrhosis before and after a LT as basal ganglia abnormalities seen in cirrhosis decrease after LT, but are still evident after 6 months following the LT procedure (Naegele et al., 2000). Lastly, the findings presented in Mechtcgeriakov et al. (2004) study highlighted an inconsistent and slowed improvement in visuo-constructive ability of their participants who underwent an LT an average of 21 months prior to testing. These studies along with the current study highlight that ESLD associated visuo-construction do not reverse completely and therefore should be continuously monitored as part of the post-transplant rehabilitation process of patients who have undergone a LT (Campagna, Biancardi, Cillo, Gatta & Amodio, 2010).

Even though the persisting deficit in visuospatial construction is mild it can have significant and frustrating consequences for the patient. Deficits in visuospatial perception can have dire implications on daily functioning such as on driving, cooking, working and dressing. Previous research reports have emphasized the role of MHE and patients with ESLD who are increasingly involved in car accidents due to fatigue, driving errors and an overestimation of driving abilities (Dubinsky & Stein, 2009; Groeneweg et al., 1998; Zhan & Stremmel, 2012). Driving errors may be caused by a deficit in visuospatial perception as visuospatial perception is required for surveillance of the roadway, traffic as well reading informational road signs (Dubinsky & Stein, 2009).

The mechanisms behind the lack of reversibility of MHE despite resolution of toxicity is unclear. Although it is suspected that other mechanisms may be implicated in the persistence of cognitive deficits (Garcia-Martinez et al., 2011). Autopsy and animal studies have implicated changes in neurotransmitter systems such as neuro-steroids, mono-amines and opioids in the hippocampus and frontal cortex in metabolic encephalopathy's such as MHE (Rose & Jalan, 2004; Zaneroli et al., 1987). Matsusue, Kinoshita, Ohama and Ogawa (2005) found that the superior parietal and posterior frontal convexities are most significantly affected by MHE in cirrhotic patients. As the neuronal basis of visuospatial construction has previously been found to be associated with the parietal portion of the dorsal stream it is plausible that irreparable neuronal cell damage has occurred in the parietal lobe caused by excess toxins (Meyer-Lidenberg et al., 2004). The relationship between MHE, visuospatial construction and the parietal lobe should be examined in further detail.

International studies have found that cognitive functioning improves with time following a LT (Lewis & Howdle, 2003; Vilstrup et al., 2014). The current study found a positive association for the length of time since an LT and cognitive performance on the RBANs test. As time passes since an LT so cognitive functioning improves on measures of the RBANs.

Yet, an association was not found for the length of time that had passed and cognitive performance of the Stroop Effect Test and the CTMT. This unexpected finding is likely to be as result of test sensitivity, the small sample size or a difference in test sensitivity between the RBANs, the Stroop and the CTMT.

A relationship was tested for a change in cognitive performance and the cause of LD. It was found that the cause of LD was not related. This was not as expected as several prior studies have concluded that the neurotoxic effect of alcohol is one of the pre-LT factors that lead to more advanced neurological injury as it causes additional cognitive deficits such as increased memory deficits (Garcia-Martinez et al., 2011).

As psychological distress can have a negative additive effect on cognition, the participants were tested for psychological distress using the BSI-18. The somatisation score was found to be related to the language score of the RBANs.

The depression score was found to be correlated to the visuospatial construction score and immediate memory of the RBANs test as well as the Stroop effect test scores which measure executive functioning. In mood disorders such as depression, cognitive impairment can be severe and global often imitating dementia. Depression is commonly found to be related to impaired performances in memory, visuospatial functioning and executive functioning. It has been highlighted that as cognitive deficits increase so the symptoms of the mood disorder increase (Trivedi, 2006). Therefore, a finding for a correlation between the domains of immediate memory, visuospatial construction and executive functioning was expected.

The anxiety score was found to correlate with the attention score of the RBANs test. A relationship between anxiety and attention has previously been discussed in detail.

Comparison between groups with and without LT

Research question 4 of the present study focused on comparing cognitive functioning between patients who have had a LT and those who are currently waiting for an LT to further determine the role of an LT on cognitive functioning as well on psychological distress. Firstly Research Question 4 involved applying an Ancova statistical technique to compare the mean scores of each of the cognitive functioning indices after controlling for a difference in pre-test scores. The study did not reveal consistently significant difference in scores across all cognitive tests. A significant difference was found only in the RBANs attention index as well as for the Stroop Effect Test scores. A significant difference was not seen for the RBANS index scores of immediate memory, visuospatial construction, language, delayed memory. Neither was there a difference in CTMT scores for patients who have had an LT and patients yet to undergo a LT. These results were similar to the results highlighted by research question 3 in which cognitive performance was compared between the two.

Psychological Distress

Research question 4 involved applying a Mann Whitney U test found that patients who have undergone a LT did not have a different psychological profile in comparison to patients who are awaiting an LT. This was an unexpected result as several previous studies have reported a significant improvement in patients who have undergone a LT in contrasts to patients awaiting an LT (O'Carroll et al., 2003; Bryan et al., 1998; De Bona et al., 2000).

However as both participants have psychological stress. Patients on the waiting list to receive an organ are likely to have fear owing to the uncertainty of the time spent waiting for a liver as well as the awareness of the paucity of organ donations (De Bona et al, 2000; Diaz-Dominguez, Perez-Bernal, Perez-San-Gregorio, Martin-Rodiguez, 2006). Whereas, patients who have had a LT experience psychological distress over accepting a new organ, fears of

organ rejection, compliance with stringent immunosuppressant medication, adaption to changed social relationships and occupational settings and sometimes even post-traumatic stress following surgery (Gover & Sarkar, 2012). However, the BSI-18 did not explicitly assess psychological distress related to their situation, rather it ask general, questions such as "have you in the last 7 days felt blue?" and "have you in the last 7 days felt weak in parts of your body." Given that 13 of the participants have a serious illness and that the remaining 18 participants have recently undergone life threatening surgery (an average of a year prior to testing), it may be, for future studies, pertinent to grasp a better understanding of the patients emotional states based on their situation.

Management of MHE and Psychological Distress

Currently, there is no known method for the prevention or cure of MHE. Therapy for MHE focuses primarily on the gut as MHE is thought to arise from the proliferation of ammonia from the liver. Commonly MHE is managed with a combination of pharmacological and dietary therapies. Pharmacological treatments include 3-6 months of non-absorbable disaccharides therapies such as lactulose and lacticol. These have been found to decrease blood ammonia levels and consequently improve psychometric performance (Kale et al., 2006; Prasad, Dhiman, Duseja, Chawla, Sharma & Argarwal, 2007). Additional pharmacological treatments include branched-chain amino acids, L-ornithine L-aspartate, flumazenil and acetyl L-carnitine. Dietary therapies have been suggested. These involve eating roughly 1.2kg of vegetable based protein daily as well as taking prebiotics, probiotics (commonly found in yogurt) and synbiotics (Liu et al, 2004). Liu and colleagues (2004) revealed in their study that synbiotic treatment to a cohort of patients with liver cirrohosis decreased the severity of ESLD, reduced blood ammonia levels in 50% of the patients.

Although, the aforementioned pharmacological and dietary treatments significantly improve MHE, these therapies neither prevent not cure MHE. A recurring comment made by patients during the interview process of the current study emphasised a great perceived concern of the patients taking additional pharmacological medication on their weakened immune system and/or presently poor functioning liver. A possible alternative is neurocognitive rehabilitation which may increase cognitive functioning of patients whilst they are awaiting a LT therefore reducing the possibility of the patient developing overt HE as well as further restoring cognitive functioning after a successful LT.

Neurocognitive rehabilitation refers to a systematically applied set of medical and therapeutic services designed to improve cognitive functioning and participation in activities that may be affected by difficulties in one or more cognitive domains (Wilson, 1997). There are four main approaches to neurocognitive rehabilitation. Firstly, the cognitive retraining approach is based on the assumption that remediation of cognitive deficits can be achieved by exercise, practice and stimulation. Secondly, the cognitive neuropsychological theoretical approach highlights the importance of identifying the nature of the deficit and using a cognitive theory to select a treatment programme. The third method is the combined approach which involves analysing the problem, assessing its everyday manifestations and difficulties often using formal behavioural and cognitive theoretical approaches. Lastly, the holistic approach is concerned with not only cognitive deficits caused by insult to the brain but focuses on emotional, psychosocial and behavioural deficits which results in a widespread effect on safety, functional independence, productive living and social interaction (Wilson, 2008; Wilson, 1997).

Due to the multi-deficit nature of MHE, which include deficits in cognitive functioning, emotional functioning, quality of life that result in problems in everyday living, for patients, a holistic neurocognitive rehabilitation program is suggested to provide a gold standard of care

for patients with ESLD. Additionally, Prigatano (1999) suggests that rehabilitation is likely to fail if emotional issues are not dealt with. Although the author did not find a previous study in a literature search which details a link between improved cognitive functioning in patients with ESLD who have received psychological care, previous studies in individuals with cognitive deficits have revealed an association in this regard.

Neurocognitive rehabilitation may be a potentially successful solution to MHE. However, neurocognitive rehabilitation is tremendously lacking within the South African context. This is due to, in a large part, to the lack of a registered category of neuropsychology which results in a scarce number of trained professionals who can provide care for patients with cognitive deficits. Therefore, limiting the care that can be provided to patients.

Limitations of Study

The present study has several limitations which may affect the results of the research as well as influence the implications of the research. Although this may diminish the generalisability of the study to the South African context and other contexts it allows for improvements in future research in the domains of MHE in patients with ESLD.

The current study involved a small sample size which may reduce the statistical power of the study. A study with a low statistical power has a reduced chance of discovering a true effect however it reduces the probability that a statistically significant result represents a true effect (Button et al., 2013). Thus, the results may not be representative of the population as they could have produced a false significant/non-significant result, whereas a bigger sample would eliminate this predicament, although it would be increasingly difficult to obtain.

The study employed a non-probability convenience sampling strategy, which may have produced confounding results as it may possibly cause a systematic sampling error. A systematic sampling error is defined as a bias in measurement strategies created by

convenience sampling (White & McBurney 2012). Research using convenience sampling strategies have found that people who volunteer have different characteristics from the population from which it was drawn (Bellini & Rumrill, 2009). Rosnow and Rosenthal (1976) found that people who volunteer for research tend to be better educated, of higher social class, more intelligent, more sociable and require more social approval. In evaluating a volunteer sample the researcher should consider how likely it is that individuals who volunteer for the current study are different to those that did not (Bellini & Rumrill, 2009). Moreover, the WDGMC is a privatised hospital which attracts a different sector of the population than the government hospitals Charlotte Maxeke Johannesburg Academic Hospital and The Chris Hani Baragwaneth Hospital. It is probable that the patients at the WDGMC shall typically belong to a middle to upper SES, gone to resourced schools and be more westernised than patients who go to Charlotte Maxeke Johannesburg Academic Hospital and The Chris Hani Baragwaneth hospital.

A further limitation concern pertains to the content of the neuropsychological test battery. Both practical time constraints as well as stamina limitations due to the patient's medical condition necessarily prevented an in-depth quantitation of all neurocognitive processes. It is plausible that test fatigue resulted in a lower score in the later tests. It is, therefore, essential that the findings reported herein are not over-generalized to assume recovery across all cognitive processes.

The author of the study acknowledges that cognitive functioning is influenced by several factors that are present prior to and following on from a LT. Some of these may not have been adequately recognised within the study. This has implicated a further limitation pertaining to the tests batteries is that the current study did not employ currently standardised South African norms of the test batteries to compare the sample to. This is highly problematic as cognitive performance is dependent on the environmental context. Culture is therefore a

moderating variable of assessment. Increased awareness of the extent to which an individual's traditions and practices may contribute to the findings need to be understood in future, especially in interpreting the test results. Such variables include ethnicity, age, cultural background, immigration patterns, quality and level of education, acculturation, bilingualism, and socioeconomic status. Furthermore, given that human brains are "plastic," recurrent active and long term cultural engagement results in modified neural pathways in the brain (Kitayama & Uskul, 2011). Consequently, by employing a test which as to date is not standardised to a multicultural environment creates a bias. Bias threatens the validity of an instrument applied across different cultures (Tanzer, 1997 as cited in Vijver & Tanzer, 2004).

Recommendations for Future Research

In contrast to other contexts, especially concerning the United Kingdom and the United States, South Africa is conducting an inferior number of valuable studies to such an extent that South African hospitals, barring for WDGMC are not examining measures of MHE. Furthermore, at present the current study is one of the only studies that has been conducted within the South African context. Subsequently, there is a vast range of various areas in which research could focus on.

A future longitudinal study should focus on examining the neuropsychiatric progression of MHE to overt HE every six months until such a time that the patient can have surgery. Following LT, the patient's neuropsychiatric status should be examined at 6 months post-surgery as well as 12, 18 and 24 months after to track the change and improvement of the patient's cognitive status. This would provide researchers and medical professionals in South Africa an idea of the time period it takes for a patient to fully restore their cognitive functioning, if ever. This study could also re-test patients at 5 years and 10 post surgery so as to gleam the full clinical picture of the reversibility of MHE following a successful LT.

Additionally, future studies could be lead to assess the effectiveness of different neurocognitive rehabilitation programmes which focus on improving the areas which are affected by MHE. This could be done both pre-transplant and post-transplant. For pre-transplant patients this could result in revealing an effective way to delay cognitive decline whilst awaiting for a transplant which may reduce the probability of a patient developing overt HE. For patients who have been transplanted this may result in limiting the time it takes for the individual's cognitive performance to recover as well as improve the cognitive performance above the plateau of current recovery.

It is vital that for future studies to be conducted within the South African context that a study is undertaken to create normative data for the RBANs test. This is largely due to the necessity to recognise that cognitive functioning reflects the context and the environments that people engage with as important variations in cognitive functioning are as a result of the meanings, artefacts, practices and institutions that structure the environmental context.

Patients who have undergone a LT take immunosuppression medication so as to prevent the rejection of the allograft (Pillai & Levitsky, 2009). Previous studies have found that 10-28% of patients who take cyclosporine (an immunosuppressant) experience some form of neurotoxic adverse event (Bechstein, 2000). These may include a host of sensory motor deficits, minor symptoms comprise of tremors, neuralgia, and peripheral neuropathy whereas severe symptoms include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or leukoencephalopathy (Bechstein, 2000). A prospective study may wish to measure the neuropsychological effects of immunosuppressants. However, causal studies such as this would have to consider the pre-transplant status of the recipient, post-operative complications as well as the additive effect of the several drugs patients have to take (Bechstein, 2000).

Furthermore, Bechstein (2000) made the observation that different personality types may present with varying susceptibility to neurotoxic side effects, psychological assessment of patients may be a factor in determining the best drug regimen to use in order to avoid neurotoxic adverse events. Further studies are needed to assess this observation to provide empirical evidence.

A plausible prospective study within the South African context may wish to examine health related quality of life for patients diagnosed with MHE. Previous international studies have revealed that health related quality of life is impaired in patients with MHE which may place a further social and economic burden on the health providers and care givers. Furthermore, a future study may wish examine whether differential levels of psychosocial support is related not only to successful transplantation and quality of life but additionally improved cognitive functioning.

Conclusion

In summary, this exploratory study identified the current picture of MHE within the South African context. The present study began by examining the sample of patients compared to the population of patients from the WDGMC. This was inspected as the sample of patients selected for the study had all similarly been carefully chosen to be placed on the waiting list for a LT whereas the population included patients who were deemed unfit to be placed on a waiting list and therefore would not receive a LT. Therefore, it was necessary to examine the plausible differences between the sample and the population. The study revealed that there was not a significant difference for any of the measures except for education. Education can significantly affect cognitive functioning as education not only increases cognitive reserve, but also strengthen the skills tested by neuropsychological assessments. However, as the cognitive scores did not reveal a difference, it is possible that disease severity is the superseding contributor to cognitive deficits in patients with ESLD.

The second aim of the study targeted at investigating the natural progression of MHE on a sample of 13 participants from the WDGMC. The current study revealed that there was not a significant change in cognitive functioning between the patient's initial test and the follow up test for immediate memory, language, visuospatial construction and delayed memory. However, there was a significant decrease in attention and processing speed. As attention is reliant on processing, it is plausible, that processing speed is the main pathological deficit of MHE.

Thirdly, the study aimed at investigating the role of a LT on cognitive functioning. Through the study it was found that while individuals who have had ESLD show an improvement in the indices of attention and delayed memory of cognitive functioning there are residual deficits in visuospatial construction which are still apparent 11.6 months after surgery. The

improvement in cognitive functioning was found to be related to psychological distress as well as the length of time since the LT.

Lastly, the study compared 13 patients who are currently on the waiting list for a LT and have taken a cognitive profile follow-up to the 13 patients who have undergone a successful LT and have completed follow up since surgery. An Ancova controlling for pre-test scores revealed that patients who have undergone a LT have significantly higher scores in attention compared to the patients awaiting a LT. Yet, they do not score differently on indices of immediate memory, language, visuospatial construction and delayed memory. As visuospatial construction is the only index that showed a persistent cognitive impairment, there is a justification that visuospatial construction does not improve with a LT. Furthermore, the study found that both patients on the waiting list as well as those who have undergone a LT have psychological distress which was related to the cognitive functioning.

Finally, patients have been found to display progressive cognitive deficits, with the patients awaiting a LT. Patients were also found to have residual cognitive deficits, with the patients who have undergone a successful LT. The patients additionally have psychological distress. Thus, it is necessary for patients to receive neurocognitive rehabilitation which simultaneously focuses on psychological functioning as well as the cognitive deficits the patients with ESLD at the WDGMC are showing.

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Appendices

Appendix A - DSM 5 Criteria Depression

A. Five (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Appendix B – Post Traumatic Stress Disorder Criteria

A. The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: **(one required)**
    1. Direct exposure.
    2. Witnessing, in person.
    3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
    4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.

B. The traumatic event is persistently re-experienced in the following way(s): **(one required)**
    1. Recurrent, involuntary, and intrusive memories. Note: Children older than six may express this symptom in repetitive play.
    2. Traumatic nightmares. Note: Children may have frightening dreams without content related to the trauma(s).
    3. Dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness. Note: Children may reenact the event in play.
    4. Intense or prolonged distress after exposure to traumatic reminders.
    5. Marked physiologic reactivity after exposure to trauma-related stimuli.

C. Persistent effortful avoidance of distressing trauma-related stimuli after the event: **(one required)**
    1. Trauma-related thoughts or feelings.
    2. Trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

D. Negative alterations in cognitions and mood that began or worsened after the traumatic event: **(two required)**
    1. Inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs).

2. Persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., "I am bad," "The world is completely dangerous").
3. Persistent distorted blame of self or others for causing the traumatic event or for resulting consequences.
4. Persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest in (pre-traumatic) significant activities.
6. Feeling alienated from others (e.g., detachment or estrangement).
7. Constricted affect: persistent inability to experience positive emotions.

E. Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: **(two required)**
    1. Irritable or aggressive behaviour
    2. Self-destructive or reckless behaviour
    3. Hypervigilance
    4. Exaggerated startle response
    5. Problems in concentration
    6. Sleep disturbance
F. Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.
G. functional significance. Significant symptom-related distress or functional impairment (e.g., social, occupational)
H. Disturbance is not due to medication, substance use, or other illness. *Specify if*: With dissociative symptoms.

In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:

1. **Depersonalization**: experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to me" or one were in a dream).
2. **Derealization**: experience of unreality, distance, or distortion (e.g., "things are not real").

Specify if: With delayed expression.

Appendix C – Generalised Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): Note: Only one item is required in children.

   1. Restlessness or feeling keyed up or on edge.
   2. Being easily fatigued.
   3. Difficulty concentrating or mind going blank.
   4. Irritability.
   5. Muscle tension.
   6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism)

F. F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder social phobia, contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder)

Appendix D – Somatisation Disorder Criteria

A. Somatic Symptoms: One or more somatic symptoms that are distressing and/or result in significant disruption in daily life.

B. One or more of: Excessive thoughts, feelings, and/or behaviors related to these somatic symptoms or associated health concerns:

    1. Disproportionate and persistent thoughts about the seriousness of one's symptoms
    2. Persistently high level of anxiety about health or symptoms
    3. Excessive time and energy devoted to these symptoms or health concern

C. Chronicity: Although any one symptom may not be continuously present, the state of being symptomatic is persistent and lasts > 6 months.

Appendix E – Transplant Questionnaire

Demographic information

Name:

Surname:

Gender:

Date of birth:

Occupation:

Level of Education:

Marital Status:

Liver disease diagnosis

What was your diagnosis/ what is it called?

What medication do you take?

Transplant patient

Date of transplant:

Briefly tell me how you found the experience

How are you feeling physically since your transplant?

Fatigue:

Nausea:

Itching:

Other:

How are you feeling emotionally since your transplant?

Anxious:

Depressed:

Sleep:

Appetite:

Libido:

Has there been anything you have found to be particularly difficult since your transplant?

Have you noticed any changes in attention, orientation, memory, walking reading, writing

Appendix F– Questionnaire for the Non-Transplant group

Demographic information

Name:

Surname:

Gender:

Date of birth:

Occupation:

Level of Education:

Marital Status:

Liver disease diagnosis

What was your diagnosis/ what is it called?

What medication do you take?

Non Transplant Patient

Last testing date

Are you waiting for a liver transplant?

If no, do you know why you were rejected from having a liver transplant?

How are you feeling?

Would you say your mood is stable?

yes

No/ Labile

What precipitates change in mood

How have you been sleeping?

Normal

Stable

Poor

Restless

Insomnia (early, middle, late)

Reversal of sleep patterns (day and night)

What keeps you awake?

Has there been anything you have found to be particularly difficult?

Have you noticed any changes in attention, orientation, memory, walking reading, writing

Have you had an episodes of confusion?

Appendix G – RBANs Test Content

The content of the RBANS consists of neurocognitive test paradigms that are familiar to neuropsychologists, and well-validated in many contexts elsewhere. The subtests are described below:

Immediate Memory

- List Learning: This consists of a list of 10 unrelated words, read for immediate recall over four trials, for a total maximum score of 40. The words are of moderate-high imagery and low age-of-acquisition, thereby reducing possible education effects on performance and easing translation.
- Story Memory: This consists of a 12-item story, read for immediate recall over two trials, for a total maximum score of 24. Scoring is based upon verbatim recall, and the stories contained in the different forms of the RBANS follow the same basic structure.

Visuospatial/Constructional

- Figure Copy: This consists of the direct copy of a complex geometrical figure, similar to the Rey-Osterrieth figure, but somewhat less demanding. There are 10 components of the figure, and a structured simplified scoring guide (contained on the record form) yields a maximum score of 20. There is an additional detailed scoring guideline and associated transparency available as of 2008 to improve inter-rater reliability in scoring this subtest (this is the only subtest for which scoring is not entirely objective).
- Line Orientation: Subjects are shown an array of 13 lines, fanning out from a common point of origin through 180 degrees. For each item, two target lines are shown beneath the array, and subjects must identify which lines they match within the array. There are 10 items, each containing two lines to be matched, for a total maximum score of 20.

Language

- Picture Naming: This is a confrontation naming task, with 10 line drawings of objects that must be named by the subject.
- Semantic Fluency: Subjects are given 60” to provide as many exemplars as they can from a given semantic category (e.g., fruits and vegetables).

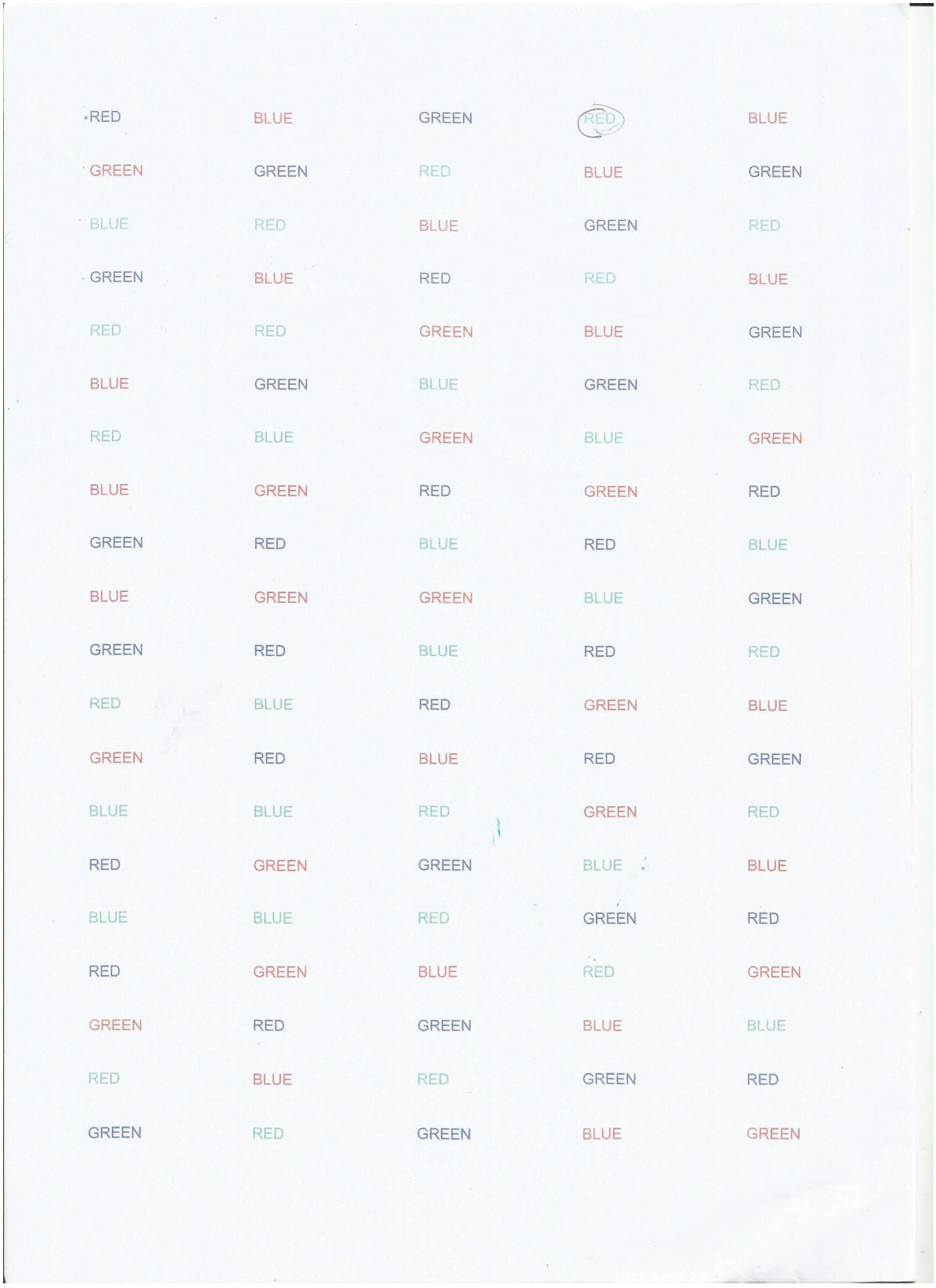
Attention

- Digit Span: This is a classic digit repetition test of working memory, with stimulus items increasing in length from 2 digits to 9 digits. Items are administering in order of length, and the test is discontinued after failure of two items at a given string length.
- Coding: This processing speed subtest is very similar to the Digit Symbol subtest of the Wechsler scales. Subjects must fill in digits corresponding to shapes as quickly as they can on the basis of a coding key. After completing practice items, subjects have 90" to complete as many items as they can.

Delayed Memory

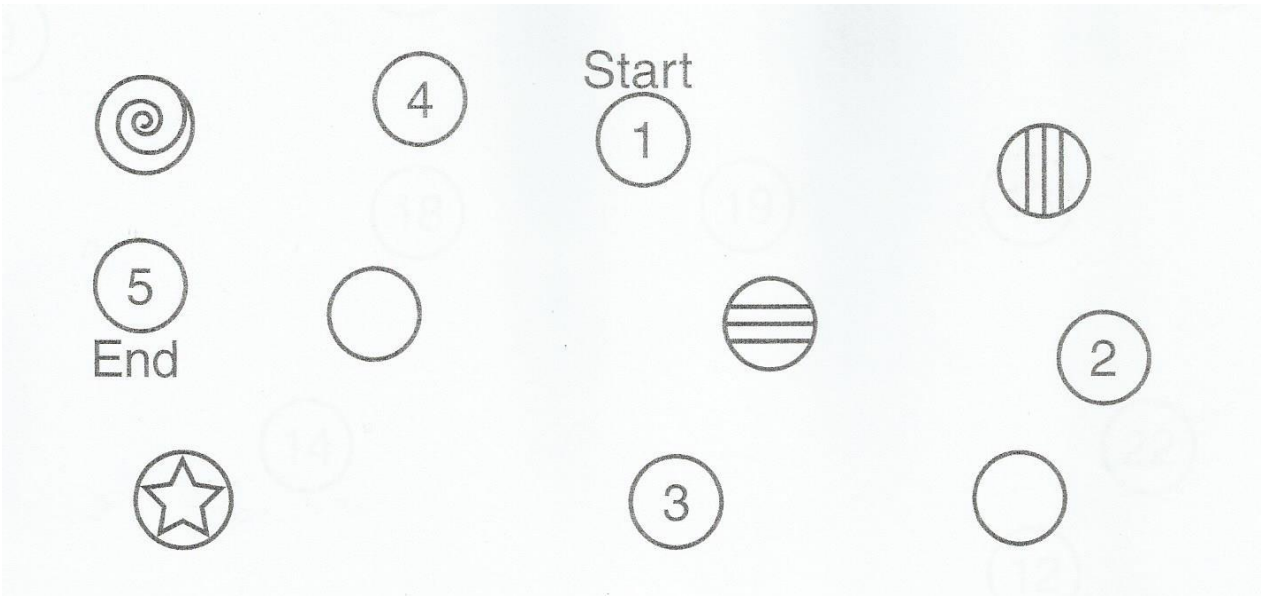
- List Learning Free Recall: Free recall of the words from the initial List Learning subtest (max=10).
- List Learning Recognition: Yes/No recognition for the words from List Learning, with 10 foils (max=20).
- Story Memory Free Recall: Free recall of the story from the Story Memory subtest (max=12).
- Figure Free Recall: Free recall of the Figure from the Figure Copy subtest (max=20).

Appendix H – Example of a Stroop Test



RED	BLUE	GREEN	RED	BLUE
GREEN	GREEN	RED	BLUE	GREEN
BLUE	RED	BLUE	GREEN	RED
GREEN	BLUE	RED	RED	BLUE
RED	RED	GREEN	BLUE	GREEN
BLUE	GREEN	BLUE	GREEN	RED
RED	BLUE	GREEN	BLUE	GREEN
BLUE	GREEN	RED	GREEN	RED
GREEN	RED	BLUE	RED	BLUE
BLUE	GREEN	GREEN	BLUE	GREEN
GREEN	RED	BLUE	RED	RED
RED	BLUE	RED	GREEN	BLUE
GREEN	RED	BLUE	RED	GREEN
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	GREEN	BLUE	BLUE
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	BLUE	RED	GREEN
GREEN	RED	GREEN	BLUE	BLUE
RED	BLUE	RED	GREEN	RED
GREEN	RED	GREEN	BLUE	GREEN

Appendix I – Example of a trail from the CTMT



Appendix J – BSI

= A little bit 2 = Moderately 3 = Quite a bit 4 = Extremely

HOW MUCH WERE YOU DISTRESSED BY:

	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
1. Faintness or dizziness	0	1	2	3	4
2. Feeling no interest in things	0	1	2	3	4
3. Nervousness or shakiness inside	0	1	2	3	4
4. Pains in heart or chest	0	1	2	3	4
5. Feeling lonely	0	1	2	3	4
6. Feeling tense or keyed up	0	1	2	3	4
7. Nausea or upset stomach	0	1	2	3	4
8. Feeling blue	0	1	2	3	4
9. Suddenly scared for no reason	0	1	2	3	4
10. Trouble getting your breath	0	1	2	3	4
11. Feelings of worthlessness	0	1	2	3	4
12. Spells of terror or panic	0	1	2	3	4
13. Numbness or tingling in parts of your body	0	1	2	3	4
14. Feeling hopeless about the future	0	1	2	3	4
15. Feeling so restless you couldn't sit still	0	1	2	3	4
16. Feeling weak in parts of your body	0	1	2	3	4
17. Thoughts of ending your life	0	1	2	3	4
18. Feeling fearful	0	1	2	3	4

Test Administrator: To begin scoring, tear off this perforated strip and follow the directions on page 7

page and follow the directions for completing the additional information.

Page 3

Page 5

Appendix K – Informational Letter from Dr Sideris

Dr. Tina Catherine Sideris
Clinical Psychologist

(MA Wits; D Litt et Phil Rau)
PS 0029734
PR 8617821

Donald Gordon Medical Centre **083 518 0070**
18 Eton Road **011 356 6045**
Parktown 2193 **e-mail:** tinanded@icon.co.za

Dear patient,

Re: Follow up psychological assessment

I would like to take this opportunity to introduce you to Ms Jenna Hill who is working under my supervision. Jenna is presently registered as a Masters student in the Psychology Department at Wits University.

She has a special interest in neuropsychology and as her Masters Research Project she is looking at cognitive functioning and psychological distress in patients who have had liver transplants and in patients who are on the waiting list for transplant.

Jenna will repeat the assessment we did at your first consultation with me. We will then compare the results. She will be seeing approximately 40 patients.

By participating you will be contributing to building a body of knowledge on cognitive functioning in liver disease patients in South Africa. We believe that this research will ultimately inform treatment and management of patients.

Thank you for your co-operation.

Should you have any questions please don't hesitate to contact me. My phone numbers and email address are in the letterhead.

Best Regards
Tina Sideris

Appendix L – Informational Letter from Dr Song

PROF E SONG
FCP (SA); FRCP (London)

SPECIALIST PHYSICIAN

WITS DONALD GORDON MEDICAL CENTRE
18 Eton Road, Parktown, 2193

Tel: (011) 356-6488 Pr. No. : 1803999 Fax: (011) 482-1170

Cell: 082 452 1784

Re: Participation in study "Neurocognitive Profile of Liver Transplant Patients in South Africa".

I am informed about the above study to be carried out by MA Psychology student, Jenna Hill from University of the Witwatersrand. The research has been cleared by the Medical Ethics Committee (HREC) and is approved by the CEO of WDGMC. The student is being co-supervised by Dr. T. Sideris, who sits on the Liver Transplant Panel at WDGMC.

Your participation in the study will make an important contribution to research on liver transplantation in South Africa with data that can inform the treatment and management of patients. Your participation is completely voluntary and non-participation will in no way affect your treatment.

Yours sincerely



Professor E. Song

Appendix M: Medical Ethics Clearance

R14/49 Jenna Hill and Tina Sideris

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140606

NAME: (Principal Investigator)	Jenna Hill and Tina Sideris
DEPARTMENT:	Psychology Wits Donald Gordon Medical Centre
PROJECT TITLE:	Cognitive Functioing and Psychological Distress in Patients with Liver Disease
DATE CONSIDERED:	27/06/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Enid Schutte
APPROVED BY:	Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/07/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix N – Informational Letter and Informed Consent Transplant Patients

School of Human & Community Development

University of the Witwatersrand
Private Bag 3, WITS, 2050

Tel: (011) 717 4500 Fax: (011) 717 4559

Dear Patient,

My name is Jenna Hill. I am currently completing my Master's degree in Psychology at the University of Witwatersrand. For my research study, I am interested in looking at the subtle changes in brain functioning and mood that have been caused by liver disease. I would like to invite you to take please take part in my study titled "Cognitive functioning and psychological distress in patients with liver disease." The following leaflet will provide you with information about the study so that you can make an informed decision about whether to participate in the study or not. If you have any questions that are not fully explained in this document, please do not hesitate to ask the researcher. Your participation in this study is entirely voluntary and you may stop at any time without stating a reason for your withdrawal

When you initially came to see Dr. Sideris you had 4 tests done the Repeatable Battery for Neuropsychological Status, Stroop Effect Test, Cognitive Trail Making Test and the Brief Symptom Inventory. I would firstly like to ask your permission to use the results of those tests. I would also like you to please come back to the Wits Donald Gordon Medical Centre for a follow up appointment. During the appointment you will asked to please repeat the four tests which will take approximately one hour of your time. This will show if your liver transplant has made a change to your brain functioning and to your mood. This is important in guiding future evaluation processes and treatment methods so that as a patient diagnosed with liver disease you will receive the correct treatment, care and rehabilitation in all areas of your life which are affected due to liver disease.

There are no direct benefits to you. However, there will be no cost for you to have the tests done.

There are no risks to your health by taking part in this study. However, if for whatever reason you feel uncomfortable by the content of the study or depressed either during or after the interview please contact Dr Tina Sideris (083 518 0070) a clinical psychologist at the Wits Donald Gordon Medical Centre for a free consultation.

All information that we get from this study is strictly confidential. Your results, which may be reported in scientific journals or presentations, will not have any information that identifies you as a patient or as a participant in this study. Any information regarding your well-being as a result of this study will be kept in strict confidence. The data collected will be stored on a password protected database at the Wits Donald Medical Centre however your information will be coded so that there will not be identifying information stored about you. You will be informed of any finding of importance to your health but this information will not be disclosed to anyone without your written permission.

We have obtained approval from the Human Research Ethics Committee at Wits University to conduct this study. If you have any questions about your participation in regard to this aspect of the study please contact the Chairperson of the Ethics Committee, Professor P. Cleaton-Jones on 011 717 2301 or at peter.cleaton-jones@wits.ac.za.

I hope that you would like to participate in our study and if you do, please would you indicate by signing the attached consent form.

Thank you very much for considering this study.

Jenna Hill

082 3001 399

Enid Schutte

082 920 6731

Informed consent

For study titled "Cognitive functioning and psychological distress in patients with liver disease"

- I hereby confirm that I have been informed by the researcher about the nature, conduct, benefit and the expectations of the study
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a research report.
- I may, without prejudice, withdraw my consent and end my participation in the study at any time
- I have had sufficient opportunity to ask questions
- I have read and understood the contents of the information leaflet

_____

Participant's Name (Printed)*

_____ _____

Participant's signature* Date

_____ _____

Name of person obtaining consent (Printed) Signature of person obtaining consent

Appendix 0 – Informational Letter & Informed Consent Non-Transplant Patients

School of Human & Community Development

University of the Witwatersrand
Private Bag 3, WITS, 2050

Tel: (011) 717 4500 Fax: (011) 717 4559

Dear Patient,

My name is Jenna Hill. I am currently completing my Master's degree in Psychology at the University of Witwatersrand. For my research study, I am interested in looking at the subtle changes in brain functioning and mood that have been caused by liver disease. I would like to invite you to take please take part in my study titled "Cognitive functioning and psychological distress in patients with liver disease." The following leaflet will provide you with information about the study so that you can make an informed decision about whether to participate in the study or not. If you have any questions that are not fully explained in this document, please do not hesitate to ask the researcher. Your participation in this study is entirely voluntary and you may stop at any time without stating a reason for your withdrawal

When you initially came to see Dr. Sideris you had 4 tests done the Repeatable Battery for Neuropsychological Status, the stroop effect test, the cognitive trail making test and the Brief Symptom Inventory. I would firstly like to ask your permission to use the results of those tests. I would also like you to please come back to the Wits Donald Gordon Medical Centre for a follow up appointment. During the appointment you will asked to please repeat the four tests which will take approximately one hour of your time. This will show if your liver disease has made a change to your brain functioning and to your mood further. This is important in guiding future evaluation processes and treatment methods so that as a patient diagnosed with liver disease you will receive the correct treatment, care and rehabilitation in all areas of your life which are affected due to liver disease.

There are no direct benefits to you. However, there will be no cost for you to have the tests done and if you wish your transport costs will be reimbursed to the amount of R150.00.

There are no risks to your health by taking part in this study. However, if for whatever reason you feel uncomfortable by the content of the study or depressed either during or after the interview please contact Dr Tina Sideris (083 518 0070) a clinical psychologist at the Wits Donald Gordon Medical Centre for a free consultation.

All information that we get from this study is strictly confidential. Your results, which may be reported in scientific journals or presentations, will not have any information that identifies you as a patient or as a participant in this study. Any information regarding your well-being as a result of this study will be kept in strict confidence. The data collected will be stored on a password protected database at the Wits Donald Medical Centre however your information will be coded so that there will not be identifying information stored about you. You will be informed of any finding of importance to your health but this information will not be disclosed to anyone without your written permission.

We have obtained approval from the Human Research Ethics Committee at Wits University to conduct this study. If you have any questions about your participation in regard to this aspect of the study please contact the Chairperson of the Ethics Committee, Professor P. Cleaton-Jones on 011 717 2301 or at peter.cleaton-jones@wits.ac.za.

I hope that you would like to participate in our study and if you do, please would you indicate by signing the attached consent form.

Thank you very much for considering this study.

Jenna Hill

082 3001 399

Enid Schutte

082 920 6731

Informed consent

For study titled "Cognitive functioning and psychological distress in patients with liver disease"

- I hereby confirm that I have been informed by the researcher about the nature, conduct, benefit and the expectations of the study
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a research report.
- I may, without prejudice, withdraw my consent and end my participation in the study at any time
- I have had sufficient opportunity to ask questions
- I have read and understood the contents of the information leaflet

_____

Participant's Name (Printed)*

_____ _____

Participant's signature* Date

_____ _____

Name of person obtaining consent (Printed) Signature of person obtaining consent

Appendix P – Scoring Details

The RBANs was scored according to the instructions of the standardised test manual for the RBANs. The scoring for each subtest of the RBANs was scored so that 1 point was given for the correct answer, for example, for the subtest on list learning each correctly recalled word was awarded one point for four trials whereas for the figure copy subtest a point was awared for each correctly completed portion of the drawing as well as for the portions correct placement in relation to the rest of the drawing. Each subtest had a different range of points. The coding subtest had a range of 0-89 points. The list learning and semantic fluency subtests had a range of 0-40 points. The story memory, figure copy, line orientation, list recognition and figure recall subtests had a range of 0-20 points. The digit span had a range of 0-16. The story recall subtest had a range of 0-12 points. The picture naming and list recall subtests had a range of 0-10 points.

Following the scoring of each subtest, index scores are calculated. The raw total of two subtest are needed to obtain the index score. The scores are then converted in a table according to the scores and the person's age group. To acquire the immediate memory index score the total score for list learning and the total of the story memory score are found in the table. The visuospatial/constructional score is acquired by the two subtests, figure copy score and line orientation score. The language index score is achieved by using the picture naming score and the semantic fluency score. The digit span score and coding score provides the index score for attention. The delayed memory score is obtained by the addition of the list recall total score, the story recall total score and figure recall score. Following which it is converted using that score and the list recognition score.

The Stroop was scored according to the instructions found in the Stroop manual. The Stoop test yields three basic scores. The raw score is the number of completed items on each item

(the word score, the colour score and the word colour score) in the 45 seconds of allocated time. The age/education prediction score, which provides a T-score to provide an adjusted score of what the individual should be achieving. A residual score which is calculated through the subtraction of the age/education predicted score from the raw score. The residual score is translated into a T-score.

The CTMT was scored according to the instructions found in the CTMT manual. The CTMT yields a raw score, a T-score, a percentile score, a T-score sum and a CTMT composite Index. The raw score is the time taken (in seconds) for the individual to complete each trail. This score was converted into a T-score based on the participant's age and score. The T-score translates into a percentile ranked score. Additionally, the T-scores are summed and converted to a composite index t-score and percentile.

The BSI-18 was scored according to the instructions found in the BSI-18 manual. Firstly, raw scores are calculated. A score of "0" for each item indicated that in the course of the last 7 days the individual was "not at" distressed by the item. A score of "4" which emphasised that the individual was "extremely" distressed by the item. The dimensions of somatisation, depression and anxiety were then calculated by summing the 6 items which represented each corresponding dimension. Following which each of the 3 dimension of the BSI-18 were summed up to obtain a global severity score. The raw scores for the BSI-18 symptom dimensions were then converted into standardised T-scores and plotted on the appropriate profile of male or female.

Appendix Q - Tests of Normality

Pre-test Results

Kolmogorov Smirnoff Test and Skewness Coffiecients for Normality for the RBANS, CTMT and Stroop Test

		Statistic (D)	P value	Skewness Coefficient	Distribution
RBANS	Total Scale	0.150	< 0.074	1.314	Not Normal
	Immediate Memory	0.140	< 0.123	0.491	Normal
	Visuospatial Construction	0.112	< 0.200	-0.296	Normal
	Language	0.224	> 0.000	-2.839	Not Normal
	Attention	0.082	< 0.200	0.082	Normal
	Delayed Memory	0.225	> 0.000	-1.491	Not Normal
Stroop	Word	0.181	> 0.011	0.089	Not Normal
	Colour	0.103	< 0.200	-0.064	Normal
	Colour Word	0.133	< 0.173	-1.036	Not Normal
CTMT	Composite Score	0.080	< 0.200	-0.698	Normal
	Trail 1	0.128	< 0.200	-0.656	Normal
	Trail 2	0.122	< 0.200	-0.946	Normal
	Trail 3	0.103	< 0.200	-0.642	Normal
	Trail 4	0.135	< 0.158	-0.735	Normal
	Trail 5	0.117	< 0.200	-0.651	Normal

Post Test Transplant Participants

Kolmogorov Smirnoff Test and Skewness Coffiecients for Normality for the RBANS, CTMT and Stroop Test

		Statistic (D)	P value	Skewness Coefficient	Distribution
RBANS	Total Scale	0.196	< 0.065	-1.211	Not Normal
	Immediate Memory	0.181	< 0.123	-1.074	Not Normal
	Visuospatial Construction	0.145	< 0.200	0.633	Normal
	Language	0.197	< 0.062	-1.874	Not Normal
	Attention	0.164	< 0.200	-0.119	Normal
	Delayed Memory	0.261	> 0.002	-1.427	Not Normal
Stroop	Word	0.239	> 0.008	-1.311	Not Normal
	Colour	0.160	< 0.200	-1.021	Not Normal
	Colour Word	0.100	< 0.200	-0.565	Normal
CTMT	Composite Score	0.146	> 0.200	-1.139	Not Normal
	Trail 1	0.113	< 0.200	-1.162	Not Normal
	Trail 2	0.112	< 0.200	-0.696	Normal
	Trail 3	0.175	< 0.151	-1.444	Not Normal
	Trail 4	0.140	< 0.200	-0.830	Normal
	Trail 5	0.205	> 0.043	-1.652	Not Normal
BSI	Somatisation	0.180	< 0.126	-0.413	Normal
	Depression	0.251	> 0.004	0.379	Not Normal
	Anxiety	0.124	< 0.200	0.172	Normal
	GSI	0.138	< 0.200	-0.562	Normal

Post Test Non-Transplant Participants

Kolmogorov Smirnoff Test and Skewness Coffiecients for Normality for the RBANS, CTMT and Stroop Test

		Statistic (D)	P value	Skewness Coefficient	Distribution
RBANS	Total Scale	0.180	< 0.200	0.254	Normal
	Immediate Memory	0.121	< 0.200	0.132	Normal
	Visuospatial Construction	0.257	> 0.027	1.137	Not Normal
	Language	0.140	< 0.200	-0.703	Normal
	Attention	0.171	< 0.200	0.024	Normal
	Delayed Memory	0.149	< 0.200	-0.253	Normal
Stroop	Word	0.167	< 0.200	-0.093	Normal
	Colour	0.136	< 0.200	0.885	Normal
	Colour Word	0.176	< 0.200	-0.841	Normal
CTMT	Composite Score	0.193	< 0.200	-0.329	Normal
	Trail 1	0.166	< 0.200	-0.320	Normal
	Trail 2	0.164	< 0.200	0.745	Normal
	Trail 3	0.208	< 0.162	0.231	Normal
	Trail 4	0.209	< 0.156	-0.485	Normal
	Trail 5	0.182	< 0.200	-0.540	Normal
BSI	Somatisation	0.167	< 0.200	-0.337	Normal
	Depression	0.246	> 0.043	-1.863	Not Normal
	Anxiety	0.216	< 0.128	-1.902	Not Normal
	GSI	0.224	< 0.097	-1.114	Not Normal