The Impact of Liver Disease on Cognitive Functioning and Mood

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Overview

This thesis is arranged in three parts; Part 1 is the review paper and this includes a background to liver disease including prevalence, possible causes and the different stages with regards to clinical presentations. It provides an outline of some of the major complications of liver disease, including hepatic encephalopathy. A discussion of minimal hepatic encephalopathy follows, which includes a review of the literature on cognitive deficits. Possible causes are identified with implications for future research discussed.

Part 2 consists of the empirical paper: an introduction to the research presented in this thesis and the specific aims and hypotheses investigated. The methodology of the study follows which provides information about participants (patients with varying stages of liver disease) and controls. The neuropsychological tests are listed and the different cognitive domains they measure outlined. The results section presents all the major findings from the current research with a summary of how they tie in with the hypotheses. Further elaboration of the findings is given in the discussion, which also considers how the results tie in with previous studies.

Part 3 of the thesis consists of a critical appraisal of the research. It is organised in two parts: the first section is a personal reflection of the research process and discusses some of the personal experiences encountered during the study. The second section elaborates on the discussion from Part 2 and includes a consideration of research and clinical implication that have emerged from the study. An acknowledgment of the study's various strengths and limitations is included in this section.

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Part 1: Literature Review

A Critical Analysis of Research on Cognitive Deficits in Minimal Hepatic Encephalopathy

Abstract

The following review discusses some of the cognitive and functional problems in liver disease. Some medical literature is included which is consistent with difficulties reported by patients. Prevalence, possible causes, and types of liver disease are reviewed, including an outline of various complications associated with the disease. Hepatic encephalopathy (HE) is one such complication and a general background to this is given.

It has been suggested that subgroups of patients with liver disease have mild cognitive deficits and demonstrate poorer performances on neuropsychological tests compared with matched controls. This has been termed minimal hepatic encephalopathy (MHE), a syndrome that occurs in patients with liver disease without overt symptoms of hepatic encephalopathy. The full spectrum of cognitive impairment in MHE is unknown (Collie, 2005).

Research has attempted to understand the profile of cognitive deficits in patients with liver disease. Studies have investigated various areas of functioning (e.g. psychomotor skills, attention and memory) by neuropsychological testing. The main studies are presented in the review. Some of the limitations of the minimal hepatic encephalopathy hypothesis are discussed. There is some debate about possible causes of observed cognitive deficits and various psychological models including health (coping and quality of life) and clinical (mood issues) are proposed. Further research and clinical implications are also discussed.

Introduction

1.1 Background

The prevalence of liver disease in the United Kingdom is increasing and this has important medical, occupational, social and psychological implications. Previous research has shown that liver disease patients do significantly worse in psychometric tests when compared to healthy controls (Elithorn, Lunzer & Weinman, 1975; Hegedus, Tarter, Van Thiel, Schade, Gavaler & Starzl, 1984; McCrea, Cordoba, Vessey, Blei & Randolph, 1996). Patients also report reduced quality of life (Forton, Thomas, Murphy, Allsop, Foster, Main, Wesnes, Taylor-Robinson, 2003) and work-related activities (Hamster, 1982).

The term minimal hepatic encephalopathy (MHE) has been used to describe a subgroup of liver disease patients who are characterised by 'normal' mental status. This is defined by the patient's presentation in clinical practice, (e.g. a presence of effective communication, engagement, coherent speech, and an absence of noticeable cognitive disturbances, as outlined in Table 2). The medical consultant involved in the patient's care assesses this. However, patients often report subtle cognitive dysfunction and problems performing everyday tasks. Such cognitive deficits are evident upon neuropsychological testing (Ferenci, Lockwood, Mullen, Tarter, Weissenborn & Blei, 1998; Gitlin, Lewis & Hinkley, 1986). Altered cerebral functioning has also been observed (Schomerus, Hamster, Blunck, Reinhard, Mayer & Dolle, 1981).

Minimal hepatic encephalopathy is believed to be a mild form of hepatic encephalopathy (HE). This is understood as a "clinical picture that can present when damage to the brain and nervous system has occurred as a complication of liver disorders" (Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2001). It has not been

attributed to any one cause or mechanism/toxic substance but is believed to stem from the combined effect of several factors (Pantiga et al, 2001). A role for advanced ammonia levels in HE has also been identified which has been used to account for the cognitive deficits observed (Blei & Cordoba, 2001). However, the full extent of impairment and their exact cause is unknown and few studies have investigated psychological factors and prevalence of mood (e.g. anxiety and depression) in patients with liver disease.

1.2 Liver Disease and Lifestyle

The term 'liver disease' applies to many diseases and disorders that cause the liver to function improperly or stop functioning (Stone, 2004). Hospital statistics show deaths from liver disease are increasing in the United Kingdom and deaths from alcoholic liver disease have doubled in the last 10 years. The British Liver Trust (2007) has warned that the prevalence of liver disease in the United Kingdom is likely to increase dramatically over the coming years as unhealthy lifestyles take their toll. This has serious psychological implications relating to cognitive complaints, reduced quality of life and work-related activities and mental health problems.

Almost half of all clinical presentations of liver disease are alcohol related. The Alcohol Harm Reduction Project (2003) showed how 'binge drinking' accounts for 40% of all drinking occasions among men and 22% by women in the United Kingdom. Alcohol Concern (2003) have defined binge drinking as consuming over half the government's recommended number of units for a week in one session, i.e. ten units for men and seven units for women (Raistrick, 1999).

Studies have suggested that binge drinking is most characteristic of the young. The General Household Survey (2002) found that those aged 16-24 are more

likely to binge-drink, with 36% of men and 27% of women reporting binge-drinking at least once a week. There is further concern about the drinking behaviour of children and adolescents. Plant, Miller and Plant (2004) looked at trends in drinking and illicit drug use among a sample of 2032 United Kingdom school students aged 15-16 years in a cross sectional survey. Findings were compared with earlier surveys conducted in 1995 and 1999. Results showed that over 90% of respondents had consumed alcohol at some time and 75% had been 'drunk'. This was an increase compared with the two previous studies.

Binge drinking is also estimated to cost the country £20 billion a year, according to a recent government report. The study by the Prime Minister's Strategy Unit (2003) shows 17 million working days are lost to hangovers and drink related illness each year. Billions more are thought to be spent clearing up alcohol-related crime and social problems and there are 1.2 million incidents of alcohol-related violence each year. The study also shows parents with drink problems affect 1.3 million children. This can lead to a range of adverse long-term effects, affecting general development and adjustment.

Obesity is another risk factor for liver disease. In societies where inactive lifestyles are led and high calorie diets with excessive amounts of fat and sugar are consumed, problems for the future in terms of health and obesity follow. The British Cardiovascular Society (2007) warns that the prevalence of liver disease will also subsequently increase. Non-alcoholic fatty liver disease is observed primarily in developed societies and is the most common form of liver disease in the United States and world-wide, affecting an estimated 10-24% of the world population and this figure is also set to increase.

1.3 Types of Liver disease

The liver is considered the most important organ of the body after the heart, being essential for healthy body functioning. It is also the largest organ and performs a number of essential functions. For example, it neutralises germs and bacteria from the blood and produces immune agents to control infection; the liver also makes proteins that regulate blood clotting.

As proposed by Richardson (2002) the simplest classification of liver disease is acute and chronic. The definition of acute liver disease (such as acute hepatitis and acute liver failure – ALF) is based on duration, with the history of the disease not exceeding six months. Diseases of longer duration are classified as chronic (such as chronic viral hepatitis, cirrhosis). Cirrhosis of the liver is an important cause of illness and death. In 2000 it killed more men than Parkinson's disease and more woman than cancer of the cervix (Donaldson, 2001).

Donaldson (2001) further outlined how large rises in death rates from chronic liver disease and cirrhosis have occurred in most age groups. In 45-54 year olds, there has been a greater than fourfold increase amongst men since the early 1970's and a threefold increase in woman. In 35-44 year olds, the rise has been even larger: an eightfold increase in men and approaching a sevenfold increase in women. The rise of deaths from cirrhosis amongst younger people is of particular concern where binge-drinking patterns appear to be common. In 2000 cirrhosis accounted for nearly 500 deaths in men aged 25-44 years and nearly 300 deaths in women of this age group (Donaldson, 2001).

Both acute and chronic definitions of liver disease involve damage to the liver. Infection, injury, exposure to drugs or toxic compounds, an autoimmune process or genetic causes could cause this. The disease can also be categorised by the

effect it has on the liver. *Hepatitis* is an inflammation of the liver, *cirrhosis* involves scarring and progressive cell death, *stones* cause blockages, *fatty liver* and *cancer* are relatively rare but can be life threatening.

1.3.1 Hepatitis

There are two major forms of hepatitis: One in which the liver is damaged quickly and one in which the liver is damaged slowly, over a long period of time. These viruses have been named in the order of their discovery as Hepatitis A, B, C, D and E.

- Hepatitis A is spread through infected water and food and is especially common in children. Most infected people are not aware they have been exposed to the virus.
- Hepatitis B is fairly common, especially in Asia and Africa. It is still the most common cause of acute viral hepatitis in North America and Europe. Hepatitis B can be spread by exposure to blood, through sexual relations and from mother to baby.
- Hepatitis C is passed the same way as hepatitis B. Hepatitis C is less common than B, but the majority of the people who contract it become chronically infected, able to spread the infection to others and usually have chronic damage to the liver.
- Hepatitis D and E are relatively rare.

1.3.2 Cirrhosis

As outlined by the British Liver Trust (2007) cirrhosis can be understood as the medical term to describe excessive development of scar tissue (fibrosis) within the liver. When the liver is acutely damaged, some of the liver cells die and the organ regenerates itself. If, however, a *chronic* disease process damages the liver,

scarring develops. In cirrhosis of the liver, scar tissue replaces normal, healthy tissue, blocking the flow of blood through the organ and preventing it from functioning normally. In the initial stages, this process is relatively slow and progresses over many years without causing any symptoms. However, eventually excess scar tissue builds up and this begins to interfere with some of the vital functions of the liver and at this stage, it is no longer able to regenerate itself.

A number of conditions can lead to cirrhosis (The National Digestive Diseases Information Clearing House, 2003). The common causes include excessive alcohol intake, chronic hepatitis C virus infection, Non-alcoholic fatty liver disease, autoimmune chronic active hepatitis, primary biliary cirrhosis, chronic hepatitis B virus infection, inherited diseases such as Wilson's disease, Glycogen/lipid storage diseases, prolonged exposure to some drugs or toxins and diseases of blood vessels.

1.3.3 Gallstones

Cholesterol in the bile pigments (bilirubin) in the bile may form stones in the gallbladder. These stones may or may not cause symptoms and problems, depending on their size and location. If present over long periods, they may damage the gall bladder and this often causes a feeling of bloating and discomfort in the upper abdomen after meals, especially ones high in fat.

1.3.4 Obstruction

Gallstones, tumours, trauma and inflammation can cause blockages or obstructions in the bile ducts (which drain the liver). When an obstruction occurs, bile and its related wastes accumulate in the blood and the patients skin and eyes often turn yellow (jaundice). Obstructions may be chronic and cause few symptoms, but they can also be acute and even life threatening.

1.3.5 Fatty Liver

Fatty liver causes liver enlargement and abnormal liver function. The most common cause is excessive alcohol consumption. It is usually a reversible condition, resolving with abstention from alcohol. While symptoms are usually fairly mild, it may cause cirrhosis and it is seen most commonly in overweight and diabetic individuals.

1.3.6 Liver cancer

Hepatitis and cirrhosis may lead to liver cancer in some cases, but cancer from other parts of the body that spreads to the liver is more common. People who have chronic hepatitis or cirrhosis may be checked on a regular basis for cancer.

1.4 Genetic causes of liver disease

The most common genetic liver disorder is called Haemochromatosis. It involves an excess of iron and is most common in adults. There are numerous genetic liver diseases that affect children.

1.5 Signs and Symptoms

Liver disease is often discovered during routine testing. It may not cause any symptoms at first or these may be very subtle, such as loss of energy. Chronic liver disease symptoms include jaundice, dark urine and abdominal swelling due to the accumulation of fluid, itching, unexplained weight loss or gain, and abdominal pain; symptoms may not be present until the disease has reached an advanced stage. Treatment is directed at managing the complications of cirrhosis and preventing further damage to the liver.

1.6 Other Health Complications

A weak liver can be the cause of many other chronic health problems, including gallbladder problems, constant fatigue, sleep disorders, heart palpitations, skin problems, allergies, arthritis, thyroid problems and frequent fainting. In addition woman's health problems such as uterine fibroids, ovarian cysts, breast cysts, endometriosis and painful menstruation may also be the result of a weak liver.

Additionally, as outlined above, abdominal pain has been associated with liver disease/hepatitis. Palmer (2004) outlines how patients often experience abdominal pain or discomfort around the area of the liver. The precise cause of this is unknown and some medical health professionals do not attribute the pain to the actual liver itself but to other causes (i.e. pancreatitis, gallstones or inflammation).

1.7 Prognosis of liver disease

The Child Pugh (CP) or Child Turcotte Pugh Score (Child & Turcotte, 1964; Pugh, Murray-Lyon, Dawson, Pietroni & Williams, 1973) is used to assess prognosis of chronic liver disease, mainly cirrhosis. It was initially used to predict mortality during surgery but is now used to determine the prognosis, treatment and the necessity of liver transplantation.

Child Pugh scores are also used to assess severity/stage of liver disease, with Child Pugh stage C considered more severe than Child Pugh stage A (Collie, 2005; Ortiz, 2005). The assessment employs 5 clinical measures of liver disease: bilirubin, serum albumin, INR, Astrocyte function and hepatic encephalopathy. Together, these are used to calculate the number of points that determines the CP score.

This is illustrated in Table 1:

Points	CP	1 year survival	2 year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-5	C	45%	35%

Table 1: Prognosis of liver disease CP = Child Pugh Score

1.8 Hepatic Encephalopathy

As outlined above, chronic liver disease results in cirrhosis and scarring of the liver/liver dysfunction. This is often associated with many complications, including accumulation of fluid in the abdomen, bleeding disorders, increased pressure in the blood levels of the liver (portal hypertension) and a confusion or change in the level of consciousness. The latter is known as hepatic encephalopathy (HE). This is a complex neuropsychiatric condition that occurs as a consequence of acute or chronic liver disease (Rose & Jalan, 2005).

As documented by Summerskill, Davidson, Sherlock & Steiner (1956), the different neuropsychological features of hepatic encephalopathy were described centuries ago when Hippocrates stated that "those who are mad on account of phlegm are quiet, but those on account of bile are vociferous, vicious, and do not keep quiet". A number of authors have assumed that Hippocrates was describing patients with acute liver injury and that his illustrations reflect the presentation of such patients.

Today, hepatic encephalopathy is understood as a "clinical picture that can present when damage to the brain and nervous system has occurred as a complication of liver disorders" (Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2001). It is believed to

be associated with a variety of overt neuropsychiatric manifestations including personality disorders, inappropriate affective, behavioural and sleep disturbances and cognitive and psychomotor impairments (Mattarozzi, Stracciari, Vignatelli, D'Alessandro, Morelli & Guarino, 2005). Other signs can include flapping tremor (asterixis) and a decreased level of consciousness.

Wolfe (2007) proposes subtle signs of hepatic encephalopathy are observed in nearly 70% of patients with cirrhosis and that symptoms may be debilitating in a significant number of patients. Approximately 30% of patients dying of end-stage liver disease experience significant encephalopathy, approaching coma (Wolfe, 2007)

1.8.1 Grading of Hepatic Encephalopathy

Hepatic encephalopathy is graded according to four stages of severity. Early features include reversal of sleep patterns, apathy, hypersomnia, irritability and personal neglect. In later stages, delirium and coma may occur. Worobetz (2007) outlined the following features associated with each stage of severity in hepatic encephalopathy – Table 2:

Grade	Level of Consciousness	Intellectual Function	Neurological findings	EEG
1	Lack of awareness; Personality change; Day/night reversal	Short attention	Incoordination	Slowing
2	Lethargic; Inappropriate Behaviour	disorientated	Asterixis; abnormal reflexes	Slowing
3	Asleep; Rousable	Loss of meaningful Commun-ication	Asterixis ; Abnormal reflex	Slowing
4	Unrousable	Absent	Decerebrate	Very slow

Table 2: Grades of Hepatic Encephalopathy - (Worobetz, 2007)

Additionally, the evaluation of severity of persistent hepatic encephalopathy is based on the West Haven Criteria for semi-quantitative grading of mental status, referring to the level of impairment of autonomy, changes in consciousness, intellectual function, behaviour and the dependence of therapy (Ferenci, Lockwood, Mullen, Tarter, Weisenborn & Blei, 1998). Worobetz (2007) and Ferenci et al therefore present separate grading systems of hepatic encephalopathy.

1.8.2 Aetiology

The precise aetiology of hepatic encephalopathy is unknown. It is not attributed to any one cause/mechanism or toxic substance, rather from the combined effect of several factors (Jones, 2000). There is no specific biochemical test for hepatic encephalopathy.

A number of theories have attempted to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte (supporting brain cells) function. They play

an important role in the detoxification of a number of chemicals (Wolf, 2007) and alterations may prevent them from functioning normally.

Ammonia is usually converted to urea by the liver. Additionally ammonia is one chemical detoxified by astrocytes. Two factors have led to the 'ammonia hypothesis' of hepatic encephalopathy (Blei & Cordoba, 2001): first, there is a decreased amount of functioning astrocytes, resulting in fewer opportunities for ammonia to be detoxified. Secondly, *portosystemic shunting* may divert blood containing ammonia from the liver to the wider circulation of the body. Additional support for the ammonia hypothesis comes from the clinical observation that treatments that decrease blood ammonia levels can improve hepatic encephalopathy symptoms.

One argument against the ammonia hypothesis, however, is the observation that approximately 10% of patients with significant encephalopathy have normal serum ammonia levels. Furthermore, many patients with cirrhosis have elevated ammonia levels without evidence for encephalopathy (Wolf, 2007).

Another hypothesis has identified the neurotransmitter Gamma-aminobutyric acid (GABA). GABA is a neuroinhibitory substance and for 20 years, it was postulated that hepatic encephalopathy was the result of increased GABAergic tone in the brain.

1.9 Minimal Hepatic Encephalopathy

Collie (2005) and Weissenborn (1999) proposed that a mild form of hepatic encephalopathy is termed sub-clinical hepatic encephalopathy (SHE) or minimal encephalopathy (MHE). This syndrome is found in cirrhosis, yet to date it is not well understood. It is often characterised by 'normal' mental presentation (Rose & Jalan,

2004). A medical consultant involved in the patient's care assesses this at the time of clinical presentation. It is often defined as a presence of fluid and coherent speech, appropriate engagement and an absence of cognitive deficits (poor attention, concentration) or symptoms typically found in hepatic encephalopathy (Table 2).

Some confusion is associated with this definition. Despite 'normal' presentations, such patients can report experiencing subtle cognitive complaints, which can make it difficult for them to perform daily activities (Groeneweg, Quero, De Brujin, Hartmann, Essinck-Bot, Hop & Schalm, 1998). Often, these are not reported unless the patient is asked. Such patients have also demonstrated cognitive dysfunction evident upon neuropsychological testing (Collie, 2005; McCrea, Cordoba, Vessey, Blei & Randolph, 1996). This has been attributed to altered cerebral functioning (Schomerus, Hamster, Blunck, Reinhard, Mayer & Dolle, 1981).

Recent studies have suggested that minimal hepatic encephalopathy may be distinguished functionally from other clinical forms of hepatic encephalopathy, i.e. episodic and persistent encephalopathy, primarily by the absence of overt neurological symptoms, such as asterixis, flapping tremor and pronounced fluctuations of vigilance (Weissenborn, Ennen, Schmerus, Ruckert & Hecker, 2001). Traditionally the diagnosis has been limited to patients with cirrhosis of the liver.

1.9.1 Prevalence

There is a degree of confusion over the prevalence of minimal hepatic encephalopathy in cirrhotic patients. The diagnostic criterion is poorly understood and there is a lack of consensus on how it is detected, with some speculation over the relevance of the syndrome by some clinicians (Collie, 2005). Patients are typically diagnosed with minimal hepatic encephalopathy by the consultant involved in their care when they do not present clinically with overt signs of hepatic encephalopathy

(Table 2) but report mild cognitive deficits and complain of reduced abilities to perform daily tasks.

In clinical practice, there is no uniformly accepted diagnostic criterion for minimal hepatic encephalopathy. Tests used to establish a diagnosis typically include the psychometric hepatic encephalopathy score (PHES) for screening purposes. This test assesses attention and psychomotor function and consists of five paper-pencil tests that are scored by comparison with data of healthy controls. However, this test is not widely used and the initial enthusiasm with it has subsided, mainly due to criticisms of it being rather limited. For example, various components of attention and information processing considered necessary for driving/reduced risk of accidents are not directly measured. Other test batteries have been proposed which examine motor speed and accuracy, visual perception, visuo-spatial orientation, visual construction, concentration, attention and to a lesser extent, memory (Collie, 2005).

Some clinicians base diagnosis on the result of the psychometric hepatic encephalopathy score test alone (Gitlin, Lewis & Hinkley, 1986) while others consider results of neurophysical and neuropsychological testing together (Saxena, Bhatia & Joshi, 2001). Collie (2005) also outlines how there is often no clear rationale for the use of particular tests used to diagnose MHE and several studies have employed neuropsychological test batteries assessing a limited number of cognitive domains, such as attention and motor skills (McCrea, Cordoba & Vessey, 1996).

The prevalence of minimal hepatic encephalopathy can also be understood in terms of Child Pugh score. It is generally accepted that among patients with a Child Pugh stage A, better liver function is likely and few cognitive complaints are

reported. However, in patients with a Child Pugh score of B or C, (indicating more advanced cirrhosis), MHE is probably likely in approximately 50 % of them (Groeneweg, Moerland, Quero, Hop, Krabbe & Schalm, 2000).

Depending on the test or definition used, the prevalence of minimal hepatic encephalopathy has been shown to vary between 30-84% in cirrhotic patients (Groeneweg et al, 1998). For example, Saxena, Bhatia & Joshi (2001) required that some impairment be observed on any one of four outcome measures, while Das, Dhiman & Saraswat (2001) required that performance be impaired on at least two of nine psychological tests. Subsequently, inconsistencies in the diagnostic criteria and methods between studies have contributed to wide variations in the reported prevalence of cognitive dysfunction in liver disease. Hilsabeck, Perry & Hassanein (2003) found that the rate of cognitive dysfunction varied between 0% and 82% depending upon the neuropsychological tests used to identify impairment. This is also the view of Rikkers, Jenko & Rudman (1978).

It is believed that minimal hepatic encephalopathy probably predisposes individuals to hepatic encephalopathy. Cirrhotic patients with MHE more frequently develop episodes of overt encephalopathy than those without MHE. In one study, the probability of overt encephalopathy at 3 years was 56% for those with a diagnosis of MHE and 8% for those without MHE (Oritz, 2005). Mild cognitive dysfunction can be considered a precursor to overt HE, the development of which carries a poor prognosis, with survival 1-year post diagnosis of approximately 40% (Bustamante, Rimola & Ventura, 1999). Therefore, identification and treatment of individuals at risk for conversion to hepatic encephalopathy is important in preventing death among cirrhotic patients. As described in current best practice guidelines (Blei & Cordoba, 2001), there are a number of treatment options for patients with overt HE, including

dietary management, reduction of nitrogenous load from the gut, and administration of drugs that affect neurotransmission.

1.10 Neuropsychological functioning in Liver Disease

A number of studies have investigated performances on neuropsychological tests between liver disease patients and controls. Most studies have excluded patients with overt signs (e.g. tremor, psychomotor dysfunction, impaired memory) of hepatic encephalopathy. These are presented in Table 3.

Researcher	Sample Size (N)	Area of functioning studied	Findings
Weissenborn Et al. (2003)	45 early HE patients and 52 controls	Memory	Patients scored lower than controls in memory tasks
Mechtcheriakov et al. (2004)	14 cirrhotic patients and 22 controls	Visuo-motor function; visuo-constructive ability; Frontal areas; Memory; Verbal IQ	Significant deficits in visuo-motor function, visuo-constructive ability and frontal tasks.
Pantiga et al (2001)	89 cirrhosis patients; 31 controls	Memory + immediate attention/recall; Visual-motor processing + mental flexibility; General reasoning and non-verbal IQ	Cirrhotic patients showed a degree of mental impairment in all functions studied
Mattorozzi et al (2004)	23 cirrhotic patients and 23 controls	Attention, memory & language	Significant differences in attention and memory tasks
Gilberstadt et al (1980)	20 cirrhotic patients and 11 controls	Motor performance	Significant differences in motor performance
Tarter et al (1984)	17 cirrhotic patients and 15 controls	Visual perception; visual orientation; visuoconstuction; attention	Significant deficits in all cognitive areas

Table 3: Cognitive functioning in early stage liver disease patients and controls

1.10.1 Summary of Findings

The most consistent findings have shown attention deficits and psychomotor deteriorations in minimal hepatic encephalopathy. Mattarozzi, Stracciari, Vignatelli,

D'Alessandro, Morelli & Guarino (2004) found patients had significant deficits on tests of visuospatial, selective and sustained attention. Visuospatial attention was examined by Visual Matrices, Cross Out a Test and Trail Making Test (TMT) A and B; selective attention was assessed by the Stroop colour test.

Additionally, Pantiga, Rodrigo, Cuesta, Lopez & Arias (2001) assessed cognitive deficits in patients with different stages of hepatic cirrhosis and found significant differences on tests of visual motor processing and motor flexibility. Pantiga et al argued the severity of deficit was related to the degree of hepatic dysfunction. This study is one of the most important to consider given the comprehensive test battery used and the classifications of severity of liver disease acknowledged.

Another important study to consider is the one by Mechtcheriakov, Graziadei, Mattedi, Bodner, Kugener, Hinterhuber, Marksteiner and Vogel (2004). This study also investigated visual-motor deficits in patients with liver cirrhosis and found significant deficits in visual-motor function, visual-constructive ability and verbal fluency in patients with cirrhosis as compared with an age-matched control group. Other neuropsychological functions such as short and long term memory (measured by the Rey Osterreith Complex Figure test) as well as verbal intelligence did not differ significantly between patients and controls. Like the work by Pantiga et al (2004), this study assessed a fairly wide range of cognitive skills and verbal IQ.

The studies suggest that whilst motor deficits are observed in cirrhotic patients, memory functioning is less well understood. Mattarozzi et al (2004) found patients had deficits on tests of visuospatial short term memory compared with controls and Weissenborn, Heidenreich, Giewekemeyer, Ruckert & Hecker (2003) investigated whether defective memory is a feature of early hepatic encephalopathy.

They found that patients scored lower than the controls in all most tests applied (except one of spatial memory - the Rey Osterreith Complex Figure test). They concluded that patients scored lower in memory tasks predominantly because of deficits in attention and visual perception. To date, the existing data on memory function in cirrhotics are sparse and most tests applied so far have been recall tests as opposed to tests of recognition.

Research into cognitive deficits in liver disease patients can help establish specific 'patterns' of cognitive deficits, in order to inform development of test batteries for diagnosis of minimal hepatic encephalopathy (Oritz, 2005). For example, in addition to the above studies, McCrea, Cordoba, Vessey, Blei & Randolph (1996) observed a relatively selective dysfunction of attention and motor speed in cirrhotics, in the absence of impairments in general intellect, memory, language or visuo-spatial skills.

Although all of the studies above reported using patients with early stage liver disease, not all explicitly reported how this was defined or whether they had excluded patients with overt features of hepatic encephalopathy. Patients with more severe cases of liver disease may have been included, therefore. Most of the studies used patients with different types of liver disease and Child Pugh scores varied. No consistent method of diagnostic methodology for minimal hepatic encephalopathy was adopted, other than mainly excluding patients with overt HE. However, in all studies, patients were considered to be in the early stages of liver disease and were considered to have minimal hepatic encephalopathy.

Some of the studies used patients who were due to receive transplantation and measures on neuropsychological tests were taken prior to transplantation. Again, this suggests an advanced stage of liver disease that might have impacted on test

performances, thus making comparisons invalid. Further still, studies have tended to use different tests to assess cognitive and neuropsychological domains.

In summary, minimal hepatic encephalopathy is characterised by some patterns of cognitive impairment. Areas of functioning that have been adequately tested are psychomotor skills and tests of attention (although it can be argued that most neuropsychological tests measure attention). It may also affect memory, perception and constructive abilities. Less is known about the pattern of memory impairment although spatial memory appears relatively preserved.

Studies have measured different areas of functioning although few have grouped different tests into main areas such as those measuring executive functioning or information processing domains. This demonstrates inconsistencies between studies surrounding areas of functioning to be assessed and how, i.e. by which tests. Therefore, differences between studies (with regards to tests used) have made some comparisons difficult. Further still, the extent of impairment is variable because a decrease in mental activity (attention) may impair several cognitive functions. Patients with minimal hepatic encephalopathy may even exhibit 'normal' cognitive performances but overall productivity may suffer from inattentiveness and fatigue secondary to attention abnormalities (Das & Faber, 2003).

1.10.2 Type of Liver Disease and Cognitive Functioning

One criticism of research on cognitive functioning in liver disease is that studies where group classification is based on disease severity fail to differentiate between aetiologies of liver disease (Collie, 2005). However, some studies report cognitive impairment in patients with liver disease of specific aetiology and the main body of research has focused on patients with Hepatitis C Virus (HCV), Wilson's disease (WD) and Alcoholic Liver Disease (ALD).

As outlined by Collie (2005), there is as yet no consistent 'profile' of cognitive dysfunction in HCV. Again, methodological differences between studies have made generalisation of findings difficult, although one common finding is that greater disease severity is associated with greater cognitive dysfunction and patients display psychomotor impairment. Additionally, neuropsychiatric symptoms are a 'hallmark' of WD, with clinical presentation in adulthood including personality changes and neurological signs (e.g. tremor and dystonia). WD patients display mild but clearly significant impairments in many cognitive functions compared with controls and most severely affected areas are on tests of attention and motor speed.

Further to this, there is a large body of literature demonstrating an association between chronic alcoholism and cognitive dysfunction (Collie, 2005). Cognitive impairments observed in chronic alcoholics without liver disease are commonly thought to include executive functions including abstraction, planning, problem solving and working memory, while patients with the neurodegenerative Wernicke–Korsakoff's disease typically display impairments in the formation and retrieval of new memory. Despite the large number of studies of alcoholism, there have been relatively few studies specifically investigating contributions of liver disease to the patterns of cognitive changes observed in alcoholics.

Several authors have hypothesised that cerebral and hepatic consequences of alcoholism may combine to produce more severe cognitive dysfunction in ALD patients than in non-ALD patients (Collie, 2005). However a consistent finding in the literature has been that ALD and non-ALD patients display equivalent levels of dysfunction on tests of learning and memory, simple and complex attention, psychomotor function and general intellectual ability. However, Tarter, Hegedus and Thiel (1987) found that ALD patients were impaired on tests of learning/memory and

psychomotor functioning than other groups (with cirrhosis resulting from viral hepatitis).

Hilsabeck, Perry and Hassanein (2003) studied patients with chronic Hepatitis C and other types of chronic liver disease and used a brief neuropsychological testing battery. They found test scores of patients with chronic hepatitis C did not differ from those patients with other chronic liver diseases. However, there was a significant relationship between fibrosis stage and test performance, with greater fibrosis associated with poorer performance. However, both patients with and without cirrhosis exhibited cognitive dysfunction.

One consistent feature of the results from the above studies is that neuropsychological deficits have been observed in those with different types and stages of liver disease compared with matched controls. However, as yet few consistent studies have found marked differences between types of liver disease and lack of standard comparison groups in research can make comparisons of research findings difficult.

1.11 Treating Cognitive Deficits

A number of therapies have been shown to improve cognition in liver disease, including lactulose treatment, dietary protein manipulation and oral supplementation with branched chain amino acids. For example, minimal hepatic encephalopathy has been found to disappear in some cirrhotic patients after 8 weeks of lactose treatment, whereas other findings have found that MHE resolves in a lot fewer instances. In view of these mixed findings, there is currently no consensus regarding the most practical and effective treatment strategy for cognitive dysfunction in liver disease patients without overt hepatic encephalopathy.

1.12 Limitations of the MHE Hypothesis

Minimal hepatic encephalopathy remains a phenomenon that is poorly understood. While hepatic encephalopathy is a clearer, well-defined clinical entity, occurring relatively frequently in patients with liver disease, MHE is less well defined. There is no consistent, diagnostic criterion available (Collie, 2005). In clinical practice, liver consultants involved in each patient's care usually determine judgement about the existence of hepatic encephalopathy. However, there has also been some debate around the existence of MHE and in spite of some evidence indicating that the diagnosis of MHE may be important, some clinicians believe this condition is irrelevant. Research on MHE has often included liver disease patients without overt signs of hepatic encephalopathy but has not included a diagnostic measure of this syndrome.

However, it has been established that such patients with varying degree of liver disease severity, without overt signs of hepatic encephalopathy (e.g. personality disorders, inappropriate affective, behavioural and sleep disturbances and cognitive and psychomotor impairments), report cognitive alterations that can make it difficult to perform day to day tasks requiring correct cerebral function, such as driving, operating machinery and other work-related activities (discussed below). Therefore, a further understanding of the problems associated in those without overt features of hepatic encephalopathy is necessary in order to promote early identification and management of liver disease.

The cognitive profile associated with MHE is still under study. Although patients with liver disease can report cognitive alterations and difficulties performing daily tasks or work related activities, the exact range of deficits are unknown. However, research has suggested deficits in psychomotor speed and flexibility,

verbal fluency, visual constructive abilities, frontal skills and attention. All of these have been tested adequately by the studies presented in Table 3 although the research has not assessed certain domains with a variety of neuropsychological tests and have instead used one or two to assess one particular skill. Memory ability in liver disease is less well understood and deficits have been observed in verbal but not spatial memory. Short-term and long-term memory with regard to both types of memory has not been adequately assessed. Additionally, few comprehensive batteries of neuropsychological tests have been conducted and in very few studies has data been compared to an appropriate number of healthy matched controls.

As MHE is understood to predispose individuals to HE, early detection of MHE can be beneficial in order to implement specific treatment strategies. Early recognition of impairment may allow the delay of disease. An early identification of patients at initial phases of hepatic encephalopathy may improve the quality of life and the prognosis of these patients (Das & Faber, 2003).

1.13 Causes of cognitive impairment in minimal hepatic encephalopathy: biological

In patients with mild cognitive dysfunction, the cognitive alterations are less clear. It is acknowledged that abnormalities in cognitive function exist in liver disease patients and individuals with both chronic liver disease and acute liver failure may demonstrate cognitive impairments compared to controls on neuropsychological tests.

Biological explanations have been used to account for these observations and it has been suggested that similar processes occur in both hepatic encephalopathy and minimal hepatic encephalopathy. There is a degree of confusion about the precise cause of such impairment and whether processes involved in both syndromes are identical. Research has suggested that possible causes of cognitive deficits in

minimal hepatic encephalopathy are similar yet milder as those in hepatic encephalopathy (Collie, 2005). Some causes (i.e. the ammonia hypothesis, see below) are widely accepted although further research is required to make definite conclusions.

1.13.1 The ammonia hypothesis

The most popular biological explanation of MHE is the ammonia hypothesis. As outlined above, it has been suggested that ammonia levels are excessive in hepatic encephalopathy as a result of 1) malfunctioning astrocytes and lack of de-toxification of ammonia and 2) and the non-conversion of ammonia to urea by the liver). It is thought that both these processes lead to a state of chronic hyperammonemia (Blei & Cordoba, 2001) and reduced cerebral blood flow in subcortical brain regions.

Therefore, increased ammonia could effect brain functioning and result in cognitive deficits in HE (Loudianos & Gitlin, 2000; Blei & Cordoba, 2001). In MHE, it is thought that similar yet milder processes occur which leads to an increased accumulation of ammonia. Further research is required to establish the link and the precise processes involved. Although this hypothesis is widely accepted, there are some limitations associated with it. For example, there remains some doubt as to whether excess ammonia consistently results in cognitive and functional disturbances in all patients with liver disease.

1.13.2 The role of the basal ganglia and subcortical structures

Collie (2005) outlines how the cognitive abnormalities are associated with increased toxic substances, such as those occurring in overt HE. This is considered the case in WD, in which impaired copper metabolism leads to its accumulation in

the basal ganglia although other CNS areas may be affected also (Medalia, Isaacs-Glaberman & Scheinberg, 1998).

Collie (2005) suggests that the pattern of cognitive deficits in both severe and less severe stages of liver disease (observed in both memory and psychomotor functions) reflect the involvement of both cortical and sub cortical areas. This is also the view of Blei and Cordoba (2001) who proposes that ammonia accumulates in this brain region in HE. However, it is also unclear as to whether processes are similar in both HE and MHE.

1.13.3 The systemic inflammatory response syndrome (SIRS)

While transplantation appears to alleviate cognitive dysfunction in studies of mixed aetiology, few studies have investigated long-term effects of this. Other researchers (Shawcross, Raines, Wright, Damik & Jalan, 2007) argue that there is no direct correlation between ammonia concentrations and severity of MHE, thus arguing against the role of ammonia per se and that other factors may be important. They outline (Shawcross et al, 2007) that the presence of a 'systemic inflammatory response syndrome' (SIRS) can result in poorer neurological outcomes detected by neuropsychological tests.

In general, liver transplantation results in improved cognitive function for most liver disease patients. While numerous studies have now reported that cognition improves from transplantation, others have demonstrated that very subtle impairments persist for at least 10 years post transplant (Collie, 2005).

1.14 Psychological explanations

There have been few investigations into the psychological implications of liver disease. Research has been carried out into health aspects (coping or quality of life issues) and psychological/clinical factors (mood issues) of living with a physical

illness (Gleason, Yates & Philipsen, 2004; Martin, Sheridan and Younossi, 2002). However, to date little research has been carried out into living with various types of liver disease.

As outlined above, research has shown that those with different stages of liver disease have demonstrated a range of deficits in various domains of cognitive functions although the precise profile of such impairment is yet to be determined. Patients with mild forms of liver disease can complain of some mild cognitive impairment, such as reduced attention, concentration or memory. These complaints can be investigated further by neuropsychological testing which involves the administration of specific tests which measure specific aspects of functioning and often have implications for the functioning of particular brain regions (e.g. executive functioning and frontal lobes). The neuropsychological model/approach is often used to help establish particular 'patterns' of cognitive deficits observed in particular syndromes.

Collie (2005) outlined how the common symptoms of these diseases (e.g. poor quality of life, depression, and fatigue) cause a corresponding functional cognitive disturbance. For example, the most common symptom of Hepatitis C is fatigue (Goh, Coughlan, Quinn, 1999) and patients also report psychiatric symptoms including poor quality of life, depression and anxiety (Gleason, Yates & Philipsen, 2004; Kraus, Schafer & Csef, 2000). Chronic fatigue is also one of the most common and debilitating symptoms of cholestatic liver disease, affecting up to 68% of patients (Lindor, Dickenson, Baldus, 1994).

To date, studies of minimal hepatic encephalopathy have mainly investigated the impact on cognitive functioning. Although attentional deficits would explain poor test performances, MHE may also affect multiple areas of functioning, including

mood and general wellbeing. Although MHE has been associated with poor quality of life, few studies have explored this further and a clear understanding of relevant factors considered necessary for good quality of life is lacking. Additionally, in most of the studies investigating cognitive deficits in liver disease, few, if any, have taken psychological measures of mood such as anxiety or depression.

1.14.1 Quality of Life

Martin, Sheridan and Younossi (2002) proposed that a patient's quality of life is an important measure in clinical research. They propose that less emphasis should be placed on a biomedical model of health to one that incorporates how people are affected in various social and psychological implications of disease.

A few studies have investigated quality of life in chronic liver disease and in those awaiting transplantation. Hicks, Larson and Ferrans (1992) reported quality of life in chronic liver disease patients was highest for aspects related to family life and then for health and functioning. Additionally, Park, Park, Kim, Park, Hyan, Yun, Jo, Tak, Kweon, Kim, Choi and Park (2003) measured health related quality of life in patients with chronic viral hepatitis or cirrhosis. They found scores were significantly lower in the patient group than the control group and differences were more prominent in domains reflective of mental rather than physical health.

The effects of transplantation have been investigated by Belle, Porayko, Jay, Hoofnagle, Lake and Zetterman (1997) who found over 50% of recipients noted some level of distress after transplantation. The values on quality of life measures were considered comparable and somewhat lower than those found in a study of heart transplantation recipients. Patients did tend to be much happier at follow-up than at baseline, however, and their index of well-being was similar to that of the

general population. At follow up, satisfaction was greatest with marriage and family life, followed by health.

1.14.2 Everyday functioning

Groeneweg, Quero, De-Bruijn, Hartmann, Essink-Bot, Hop & Schalm (1998) analysed the impact of minimal HE on daily functioning by administering the Sickness Impact Profile (SIP) – a questionnaire consisting of 136 statements considering ambulation, mobility, body care, social interactions, alertness, emotional behaviour, communication, sleep and rest, home management, recreation and pastime or work, to 179 cirrhotic outpatients. Forty-eight patients suffered from minimal hepatic encephalopathy, while the remaining 131 patients were normal with regard to the clinical examination, psychometric test results and EEG. The authors found a diminished level of daily functioning in the patients with minimal HE reflected by significantly more impairments in all categories of the SIP.

The implications of MHE on occupational functioning are illustrated by Hamster (1982). Hamster studied blue-collar and white-collar workers with MHE and their earning capacity was compared. 73% of the cirrhotics who were blue-collar workers had an impaired earning capacity, whereas 50% of white-collar workers were fit for work in the presence of MHE. This was due to the preservation of verbal abilities that were less affected by MHE. This illustrates the importance of considerable impairment of motor performance in MHE where verbal skills remain intact.

O'Carroll, Hayes, Ebmeirer, Dougall, Murray, Best, Bouchier and Goodwin (1991) suggested subtle impairments of cognitive function may be an important cause of occupational and psychosocial morbidity in patients with chronic liver disease although further research is required to understand possible mechanisms.

Schomerus, Hamster, Blunck, Reinhard, Mayer & Dolle (1981) argued MHE had a major impact on patients' daily living and ability to perform everyday tasks. In their study, 40 cirrhotic patients without clinical signs of HE and a control group of 12 patients with alcoholic pancreatitis underwent a comprehensive psychometric examination used for expert evaluation of the capacity to drive a vehicle. Of the cirrhotic patients, 60% were considered unfit to drive, in 25% driving capacity was questionable and only 15% - all of them non-alcoholic cirrhotics – were considered fit to drive. In contrast, 75% of the patients with alcoholic pancreatitis were considered fit to drive.

However, the effect of MHE on the risk of automobile accidents is still not settled. Two studies that have evaluated driving on a real test 'on the road' have reached different conclusions. These discrepancies may be explained by differences in the characteristics of the patients and the driving tests. It is thought MHE does not affect all patients to the same extent. The impairment of attention and speed of mental processing, characteristic of MHE, affects the ability to react to hazardous situations. However, driving is a complex activity that depends on many factors, especially premorbid skills.

However, a decline in cognitive function is believed to increase the risk attention, memory and motor co-ordination, loss of concentration, drowsiness, altered sleep patterns and confusion. As yet, there are no clear guidelines as to whether patients diagnosed with MHE should carry on driving. The Driving Standards Authority (DSA) requires anyone taking a driving test in the United Kingdom to pass a theory test in additional to the practical component. From 14 November 2002, the theory test has also included a test of hazard perception skills. Due to findings suggesting patients with liver disease are more likely to be

considered unfit to drive (Schomerus, Hamster, Blunck, Reinhard, Mayer & Dolle (1981), there has been some speculation over whether those with liver disease are able to adequately identify hazards due to possible cognitive deficits

In summary, studies have shown how quality of life and work related activities are affected in liver disease and this has been attributed to cognitive deficits. It can be suggested that this has serious implications for effects of liver disease on mental health. Collis & Lloyd (1992) however outlined how this topic has been relatively neglected in the psychiatric literature.

1.14.3 Anxiety and depression

There have been some studies investigating the psychological implications (e.g. anxiety, depression) of living with an illness. For example, it is widely documented that depressive disorders are more common in patients with physical illness than in those without, with up to one-third of medical in-patients reporting mild to moderate symptoms of depression (Rodin & Voshart, 1986).

Singh, Goyowski, Wagner & Marino (1997) looked into depression in those with end stage Hepatitis C and other types of liver disorders. They found that patients with Hepatitis C were more likely to report being significantly more depressed than those patients with other forms of liver disease, although the reasons were inconclusive. However, they also found this patient group reported significantly more pain and proposed this was possibly a reason.

Forton, Thomas, Murphy, Allsop, Foster, Main, Wesnes & Taylor-Robinson (2003) proposed that patients with chronic hepatitis C (HCV) infection frequently report depression, fatigue and a perceived inability to function effectively. Several other studies have also suggested that patients exhibit low quality of life scores that are independent of disease severity (Forton et al, 2001).

MacHale (2002) postulated that there are particular issues around antidepressants in hepatic disease in that the sedative and constipating side-effects of antidepressants may precipitate or unmask sub clinical hepatic encephalopathy. This would have psychological implications, in that terminating antidepressants due to such effects might result in increased low mood.

Anxiety is a common experience in chronic illness and in those with end-stage liver disease, it is also associated with the stress of waiting for a donor organ to become available. Quality of life, work, family and social roles are all impaired and these losses may also contribute to depression. Again, most of the available research on anxiety in liver disease has tended to look at this in end-stage liver disease.

Chappell and Case (1997) looked at levels of anxiety experienced by adult liver transplant patients immediately before surgery and at potentially stressful times throughout the recovery process, and levels were high at all stages. However, it can be suggested that anxiety levels are also high in patients with less severe stages of liver disease, especially during the periods after having been given a diagnosis as this is a period where increased worry and concern about health is experienced.

The available research into liver disease has tended not to focus on the prevalence of anxiety and depression in those with less severe types of liver disease. The research has also not investigated consistently anxiety or depression levels found in patients with various stages or severities of liver disease, as determined by Child Pugh score, for example. Therefore, the prevalence of low mood/depression and anxiety remains unknown in patients with varying stages of liver disease.

To date, minimal hepatic encephalopathy is understood to be associated with poorer quality of life and increased work disability. However, as Ortiz (2005) outlines, a major challenge is separating the effects of MHE from those of the disease

causing MHE. Research has suggested MHE may have an independent effect on quality of life and can be considered mild enough that effects on basic life activities (i.e. shopping, using public transport, dressing, etc) are not anticipated. However, the observed impairments of attention, executive function and psychomotor skills may impair complex activities such as planning a trip, handling finances, gardening, performing a job or driving a car.

The influence of MHE will depend on the demands of the job, the severity of neuropsychological impairment and the possibilities to compensate for deficits. For instance, the impairment of fine motor skills that characterises MHE is critical for those who handle machinery.

1.15 Further areas for research

The precise spectrum of deficits in minimal hepatic encephalopathy remains unknown. With regard to cognition, the full extent of impairment is uncertain in those without overt signs of hepatic encephalopathy, although significant proportions of patients present with psychomotor complaints. Few comprehensive batteries of neuropsychological tests have been conducted and in very few studies has data been compared to an appropriate number of healthy matched controls, or have taken premorbid IQ levels. The cause of such observed deficits is also unknown.

As outlined above, effects of MHE have mainly been concerned with cognition, yet MHE may affect mood and feelings, particularly when considering research that has suggested poor quality of life. The effects of mood (e.g. anxiety or depression) have not been adequately taken into account and how they might impact on a patient's cognitive functioning. Therefore, the prevalence of anxiety and depression in liver disease is important to consider from a clinical perspective.

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Part 2: Empirical Paper

The Impact of Liver Disease on Cognitive Functioning and Mood

Abstract

It has been suggested that subgroups of patients with liver disease have mild cognitive alterations and demonstrate poorer performances on neuropsychological tests, compared with matched controls. Impairments on attention and psychomotor speed have been consistently demonstrated (Mechtcheriakov, Graziadei, Mattedi, Bodner, Kugener, Hinterhuber, Marksteiner & Vogel, 2004; Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2003). This has been termed minimal hepatic encephalopathy (MHE) – a syndrome that occurs in patients without overt symptoms of hepatic encephalopathy. The full spectrum of cognitive impairment in MHE is unknown, as is their cause, and biological and psychological explanations have been proposed (Collie, 2005).

The aim of the current research is to investigate the nature of cognitive deficits experienced in patients with liver disease by investigating performances on neuropsychological tests. Tests of speed/motor functioning, frontal/executive functioning, verbal and spatial memories are included in the study. Performances on all tests are compared with 1) controls and 2) between groups of patients with different stages of liver disease. Measures of depression and anxiety are also taken.

The findings show patients with liver disease have worse performances on neuropsychological tests than controls, especially with regards to executive functioning and motor speed. Deficits are not attributed to anxiety or depression. Additionally, severity of liver disease is associated with worse performances on neuropsychological tests generally, particularly tests of motor functioning and executive function. However, patients with less severe liver disease demonstrate poorer performances on tests of verbal memory than patients with more severe stages of liver disease do. Overall, the results suggest that severity of liver disease leads to

greater cognitive deficits in some domains. Implications for future research and clinical practice are discussed.

1.1 Introduction

The British Liver Trust (2007) has warned that the prevalence of liver disease in the United Kingdom is likely to increase dramatically in the future as unhealthy lifestyles take their toll. This has serious medical, occupational and psychological implications. Minimal hepatic encephalopathy (MHE) has been defined as a syndrome that is characterised by an absence of clinical signs of encephalopathy (i.e. impaired functioning, changes in reflexes, asterixis, tremors and fluctuations of vigilance), yet a presence of cognitive disturbances. These can be detected upon neuropsychological testing (McCrea, Cordoba, Vessey, Blei & Randolph, 1996). Deficits can also effect quality of life (Groeneweg, Quero, De-Bruijn, Hartmann, Essink-Bot & Schalm, 1998) and work-related activities (Hamster, 1982).

Deficits have been consistently found on tests of psychomotor abilities, attention and visuo-constructive ability (Mattarozzi, Stracciari, Vignatelli, D'Alessandro, Morelli & Guarino, 2004). However, the full extent of cognitive impairments in minimal hepatic encephalopathy, and their possible cause, remains unknown.

Cognitive changes are evident in all types and severity of liver disease and there is little doubt that they are associated with serious functional consequences for patients, including mood, overall quality of life, decreased ability to perform normal day-to-day tasks such as driving and operating machinery, as well as disruptions to the sleep–wake cycle (Collie, 2005; Schmoerus & Hamster, 1998).

1.2 Liver Disease

Liver disease is a term given to many diseases and disorders that cause the liver to function improperly (Stone, 2004). It is an acute or chronic damage, usually caused by infection, injury, exposure to drugs or toxic compounds, an autoimmune

process or by genetic defect. The disease can also be categorised as the effect it has on the liver. Hepatitis is an inflammation of the liver, cirrhosis involves scarring and progressive cell death, stones can form blockages, and fatty liver and cancer are rare but can be life threatening.

Although there are many different causes of liver disease, it is often due to excess alcohol consumption. Alcohol consumption will increase the rate of progression of cirrhosis from whatever cause. The Department of Health (2001) stated that the rising trends in death from cirrhosis seen in England are unusual compared with our European Union neighbours, and it has been recognised that heavy episodic drinking is a noticeable feature of people's social lives in the United Kingdom. This has caused the Department of Health to highlight alcohol consumption as a key in its National Alcohol Strategy in Spring 2000.

1.2.1 Prognosis

The Child Pugh (CP) or Child Turcotte Pugh Score determines prognosis of chronic liver disease, mainly cirrhosis. It can also be used to understand severity of liver disease, Child Pugh stage A is considered to be associated with better liver functioning than Child Pugh stages B and C (Groeneweg, Mooreland, Quero, Hop, Krabbe & Schalm 2000).

1.2.2 Hepatic Encephalopathy

With severe liver impairment, toxic substances normally removed by the liver accumulate in the blood and impair brain cell functioning. These toxic substances can travel directly to the brain without being modified and lead to damage to the brain and nervous system. Signs can include impaired cognition, behavioural changes, a flapping tremor (asterixis) and a decreased level of consciousness, including coma and ultimately death. These occur in hepatic encephalopathy (HE).

The instance of HE in cirrhosis patients is high – Wolf (2007) proposed signs of HE occur in approximately 70% of cases. HE seriously impairs daily functioning in both physical and psychological domains and the prognosis of HE is poor, with survival 1-year postdiagnosis of approximately 40% (Bustamante, Rimola & Ventura, 1999).

Hepatic encephalopathy is thus understood as a "clinical picture that can present when damage to the brain and nervous system has occurred as a complication of liver disorders" (Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2001). It has not been attributed to any one cause or mechanism/toxic substance but is believed to stem from the combined effect of several factors (Pantiga et al, 2001). A role for advanced ammonia levels in HE has also been identified.

1.2.3 Grading of Hepatic Encephalopathy

The clinical symptoms of hepatic encephalopathy are graded into 4 classes, with predominant respect to the disturbance of consciousness. Usually, different stages of severity are considered to correspond with different grades of hepatic encephalopathy. As outlined by Weissenborn (1999), HE grade 1 is characterised by sleep disturbances, psychomotor slowing, attention and concentration deficits. Patients with grade 2 HE present with lethargy and disorientation. Additionally, several neuromuscular symptoms like flapping tremor, ataxia and slurred speech may be observed.

In grade 3 HE the patients are drowsy, as well as showing a characteristic disturbance of speech with preservation and echolia. Grade 4 is associated with hepatic coma. Although prognosis of HE is poor, early detection can lead to more effective management and medical treatments.

1.2.4 Minimal Hepatic Encephalopathy

Minimal hepatic encephalopathy (MHE) has been considered a mild stage of hepatic encephalopathy. Patients with liver cirrhosis but no clinical signs of hepatic encephalopathy (and sometimes termed grade 0 HE – Weissenborn, 1999) have been observed to have worse performances on neuropsychological tests than controls despite a fairly 'normal' clinical presentation. However, it has also been observed that cerebral function is altered in such patients (Collis & Lloyd, 1992).

Patients with MHE can present with some cognitive complaints, making it impossible for them to perform normal day-to-day activities, such as driving and work-related activities (Schomerus, Hamster, Blunck, Reinhard, Myer & Dolle, 1981). It is also believed that MHE signifies increased morbidity and poor qualities of life in both the physical and psychological domains (Groeneweg, Quero, De Brujin, Hartmann, Essink-Bot & Schalm, 1998).

1.2.5 Prevalence and Diagnostic Criteria

It believed that minimal hepatic encephalopathy probably predisposes individuals to hepatic encephalopathy but the prevalence of MHE is understood to vary. It is generally accepted that among patients with a Child Pugh score of A (better liver function), less patients are likely to have MHE. However, in patients with a Child Pugh score of B or C, (indicating more advanced cirrhosis), MHE is probably likely in approximately 50 % of them (Collie, 2005).

There is no uniform test for the diagnosis of MHE and it usually relies on the clinical judgement of the consultant and medical professionals involved in the care of each patient. Usually, this depends on a presence of engagement, normal speech and information processing abilities (attention and concentration) and an absence of overt

symptoms associated with hepatic encephalopathy (as outlined earlier in Table 2) at the time of clinical presentation.

The Psychometric Hepatic Encephalopathy Score (PHES) test has been developed for diagnostic purposes but this battery has been criticised for being rather limited. For example, various components of attention and information processing considered necessary for driving/reducing risk of accidents are not directly measured. Therefore, inconsistencies in the diagnostic criteria and methods have contributed to wide variations in reported prevalence of MHE. It has been reported to occur in anywhere from 30% to 84% of patients with liver disease, depending on criteria used to identify it.

Nevertheless, it is now acknowledged that abnormalities in cognitive function are a common complication of liver disease and that those with both acute and chronic liver disease may demonstrate cognitive impairments on neuropsychological tests when compared with healthy, matched controls, including impairments in memory, attention and psychomotor function. Such impairment is considered mild in MHE, yet it may represent a significant complication of liver disease that may negatively impact on quality of life and normal daily activities. It is felt early identification of cognitive manifestations of liver disease is important for timing and monitoring of treatment.

1.2.6 Summary of Research Findings on Cognitive Deficits

The most consistent finding has shown deficits in attention and motor skills. For example, Mattarozzi et al (2005) found that patients with MHE exhibited reduced cognitive performance compared with controls on several attention components including selective and visuospatial attention (visuospatial attention was assessed by the Trail Making Test (TMT) A and B and selective attention was

assessed by the Stroop colour test). Similar findings have been obtained in other studies (i.e. Mechtcheriakov, Graziadei, Mattedi, Bodner, Kugener, Hinterhuber and Vogel, 2004; Pantiga, Rodrigo, Cuesta, Lopez & Arias, 2003). The impact of early stage cirrhosis on other cognitive domains, (i.e. memory and verbal fluency), are less well understood.

Therefore, the exact range of cognitive deficits in MHE is unknown. Few studies have used large batteries of neuropsychological tests, controls or measures of premorbid IQ. Other studies have also demonstrated discrepancies between self-reported deficits by patients and actual observed deficits on neuropsychometric tests. For example, several cognitive complaints (decreased attention, confusion and memory difficulties) are related to MHE but a significant number of patients do not always exhibit abnormalities on tests that measured such domains.

1.2.7 Possible Causes of Cognitive Deficits

Cognitive deficits in early stages of liver disease have been well documented and a number of explanations have attempted to offer an explanation of the underlying causes. Magnetic resonance-spectroscopy and positron emission tomography studies have shown metabolic alterations in different brain areas, such as occipital and cingulate regions which are supposed to be involved in the control of attention and in visual-motor co-ordination (Lockwood, Weisenborn, Bokemeyer & Burchert, 2002). A role for frontal lobes and sub cortical structures, involved in executive functioning and motor tasks, has also been identified.

Due to the scarring within the liver, cirrhosis leads to obstruction of the passage of blood through the liver causing portal hypertension. This is when it is difficult for blood from the intestines to go through the liver to get back to the heart. Furthermore, in liver disease, the damaged liver may not be functioning as well as it

should be so the blood that does travel through the liver may not be adequately detoxified.

The toxic substances that accumulate in liver disease and affect the brain are not well understood. It has been proposed that the cognitive alterations observed in more advanced cirrhotic patients can be attributed to increased ammonia levels. In overt HE, cognitive and behavioural changes are thought to result from alterations in neurotransmission caused by the entry of ammonia.

In MHE therefore, it is possible that cognitive abnormalities result from milder but similar pathogenic processes such as those occurring in overt HE. That is, these diseases may indirectly affect brain function, resulting in cognitive impairment. Ammonia is normally converted to urea by the liver and can cross the blood-brain barrier where it causes support cells of the brain (astrocytes) to swell.

Exact effects of ammonia on psychological functioning are poorly understood although levels of ammonia are frequently found in the environment, i.e. in various household products such as cleaners. It is also found in water, soil and air, and is a source of much-needed nitrogen for plants, animals and humans. Most of the ammonia in the environment comes from the natural breakdown of manure, dead plants and animals.

Other explanations of the cognitive deficits in MHE suggest that the presence of a systemic inflammatory response syndrome (SIRS) confers to poorer neurological outcome (Rose & Jalan, 2004) and that inflammation may be important in modulating the cerebral effect of ammonia in liver disease. Additional explanations have involved the neuro-inhibitory neurotransmitter GABA, which is found in excessive amounts in samples of those with hepatic encephalopathy. Therefore, this could play a role in the pathogenesis in minimal hepatic

encephalopathy. Other precipitating factors include electrolyte imbalance, drug use and miscellaneous factors such as infection and surgery.

An alternative hypothesis is that the additional symptoms of these diseases (e.g. fatigue, depression, impaired quality of life) cause a corresponding functional cognitive disturbance. Fatigue has been associated with hepatitis C (Goh, Coughlan & Quinn, 1999) and cholestatic liver disease (Lindor, Dickenson, Baldus, 1994). Hepatitis C patients also report psychiatric symptoms including depression and anxiety and poor quality of life (Forton, Thomas, Taylor-Robinson, Murphy, Allsop, Foster, Main J, Wesnes & Taylor-Robinson 2003). Further studies have found significant psychological distress in patients with chronic, non-alcoholic liver disease (Davis, De Nour, Shouval & Melmed, 1998).

As outlined earlier, Park et al (2003) found that patients with chronic hepatitis C had significantly lower scores on measures of health related quality of life than controls. The difference was more prominent in domains reflective of mental as opposed to physical health. Park et al also compared performances across different severity of liver disease (as determined by Child Pugh stage) and scores on domains of mental health were lower in less severe stages of liver disease (i.e. indicating poorer quality of life scores). This study therefore constitutes an attempt to understand general wellbeing across different stages of liver disease.

Further studies are required to determine the extent to which different above explanations interact and to date findings are mixed. Cordoba, Flavia, Jacas, Sauleda, Esteban, Vargas, Esteban & Guardia (2003) argued hepatitis C causes poor quality of life even in the absence of major cognitive impairment and Forton, Thomas, Murphy, Allsop, Foster and Main (2003) argued cognitive impairment can be unaccounted for by depression. As outlined above however, few of the studies investigating cognitive

deficits in liver disease have taken psychological measures of mood, such as anxiety or depression.

1.2.8 Further research possibilities

The research on liver disease and cognitive functioning to date has investigated cognitive functioning in those without overt features of encephalopathy. Few studies have used comprehensive test batteries and the precise patterns of deficits are unknown. This is important to determine however as early detection of impairments with lead to earlier management and treatment. Therefore, this is required in further research.

Additionally, research on minimal hepatic encephalopathy has mainly been concerned with cognition, yet MHE may exert effects in other areas. The impact of mood (e.g. anxiety or depression) on cognitive functioning in liver disease has not been investigated. Furthermore, an understanding of possible mood states in liver disease, as well as the kinds of deficits experienced in varying severity of liver disease (as determined by Child Pugh score) will lead to a further understanding about how liver disease exerts its effects.

The current research is a preliminary investigation into the spectrum of possible difficulties people with early stage cirrhosis experience. It is anticipated that patients will show more performance deficits on neuropsychometric tests compared with matched controls. This has been observed in previous research although the full spectrum of deficits is unknown.

Biological explanations of minimum hepatic encephalopathy include increased ammonia levels, (as in hepatic encephalopathy), and there is agreement that both syndromes are associated with similar processes. This had led to the 'ammonia hypothesis' - in MHE, it is thought that processes are less extreme and

ammonia levels are milder than in HE. Additionally, Pantiga, Rodrigo, Cuesta, Lopez and Arias (2001) argue the patterns of cognitive deficit in liver disease increase according to severity of liver disease, and that performances on neuropsychological tests will be worse in more severe cases. This suggests that as the severity of liver disease increases, the higher the accumulations of ammonia in the blood/brain support cells which can contribute to cognitive impairment in liver disease.

Therefore, it is anticipated that in the current study, the patients with Child Pugh scores of C (indicating more severe liver disease) will be more impaired on performances on neuropsychological tests compared to patients with Child Pugh scores of A (indicating less severe stage of liver disease). The proposed research will investigate the effects of early stage cirrhosis on a number of domains of cognitive functioning, to be assessed by standardised measures. Additionally, a measure of psychological functioning (anxiety and depression) will be included. Finally, a measure of premorbid IQ will be taken.

1.2.9 Study aims and hypothesis

The aim is to:

1) Identify the range, nature and extent of neuropsychological deficits through standardised/self-report measures in patients with different levels of severity of liver disease, as measured by Child Pugh scores and compared to controls;

2) Explore the association between cirrhosis and mood.

1.3 Method

1.3.1 Design

The present study is a cross sectional, between subjects study comparing neuropsychological performance in 27 patients with liver disease with 22 healthy volunteers (controls). The controls were matched to the cirrhotic group for years spent in education and estimated premorbid ability/intelligence.

1.3.2 Ethical Approval and Informed Consent

The joint UCL/UCLH committee on the Ethics of Human Research, Committee A, granted ethical approval for this research project (Appendix A) and written informed consent was obtained from participants (Appendix B).

Approval involved making an amendment to a previous study concerned with investigating hazard perception in a cirrhotic patient group. The amendment was made in order to perform the neuropsychological tests on cirrhotic patients. The hazard perception part of the study is yet to be completed. Patients were compensated for their time.

1.3.3 Participants – Patients with Liver Disease

A sample of 27 participants were studied (11 women and 16 men), mean age 54.81 years (SD = 9.05). Patients were recruited from the liver clinic at University College London Hospital. The Registrar was given the patient inclusion/exclusion criteria and forwarded on contact details of suitable patients to the researcher. All patients were receiving ongoing monitoring by the liver consultant and were diagnosed with hepatic cirrhosis, following physical and biological examinations by the consultant involved in their care at the liver clinic.

The Child Pugh score of each patient was calculated and given to the researcher at the time they were referred for the study. Once referred, patients were

contacted by telephone and the study was explained before asking whether they would like to participate in the study.

Patients were subdivided into groups according to their Child Pugh score. Accordingly, 9, 8 and 10 patients were in each of the Child A, B and C groups respectively. Cirrhosis was diagnosed by using classical clinical and analytical criteria and was confirmed by liver biopsy.

1.3.4 Exclusion criteria

Patients were excluded from the study if they had hepatic encephalopathy. The liver consultant assessed this by the absence of symptoms usually observed in HE (please see Table 2 , Part 1) before the patient was referred for the study. This was based on clinical assessment and patient self-reports of typical symptoms of HE as outlined earlier. They were also excluded if they were older than 65 years of age or had been diagnosed with any psychiatric or neurological problems. This was the responsibility of the medical registrar who checked patient files and medical notes/history before referring patients to participate in the study. On this basis, the registrar also excluded patients if they had ongoing addictions to psychotropic drugs or alcohol, cardiovascular disease, renal dysfunction, recent gastrointestinal bleeding, malignancy or pregnancy. Based on these criteria, two patients were excluded from the study.

1.3.5 Matched controls

The control group (CG) comprised 22 healthy volunteers, mean age 45.59, (SD = 10.92). This group participated in a similar study and served as a control group in a study that investigated effects of organic phosphate poisoning in farmers in 2006 in Norfolk. All control participants responded to an advertisement seeking participants for the study at that time. Data was used to serve as a comparison group

and all participants in this control group were screened for physical, neurological or psychiatric problems (determined by clinical interview before the participant was included in the study). The educational level and premorbid IQ level in the CG were similar to those in the cirrhotic groups.

1.3.6 Neuropsychological Assessment

All participants underwent detailed psychometric testing. Only well known, reliable and clinically sensitive measures were selected for inclusion in this test battery. As was mentioned in the introduction, previous studies have often used limited test batteries that 1) do not assess classes of cognitive function and 2) have not included any measures of mood.

Tests were selected which would assess a broad range of cognitive functions consisting of premorbid IQ, language skills, memory functioning (verbal and visual), information processing speed, executive function and visuo-perceptual ability. Tests were also chosen on the basis of minimal administration time. Following this, tests were clustered as follows:

1.3.7 Premorbid IQ:

The National Adult Reading Test (Nelson, 1982) was used to assess premorbid ability. This estimate of IQ is relatively resistant to organic brain damage and correlates highly with Wechsler Adult Intelligence Scale-Revised (WAIS-R) IQ scores in healthy adults (Crawford, 1989).

1.3.8 Subtests from the WAIS–R

Subtests from the WAIS-R were included, two that measure verbal IQ (Vocabulary and Digit Span) and two that measure non-verbal IQ (Block Design and Digit Symbol).

1.3.9 Memory:

The Adult Memory and Information Processing Test Battery (AMIPB: Coughlan and Hollows, 1985) was used to assess visual and verbal memory. There are four main subtests that assess memory functioning: a list learning task, prose recall (immediate and delayed), a design learning task and immediate and delayed recall of a complex figure.

For the list learning tasks, scores for overall numbers of words recalled during the tasks, as well as after a distraction, were used. Performance on the design-learning task was also assessed this way (i.e. scores for performance throughout the task and score for memory of the task after a distraction task). In both tests, distractions involved the administration of another similar task before memory for the original material was tested. For list- learning, another list was administered before test recall and in design-learning, another design was administered before recall of the original design was tested.

For the complex figure task, scores for both the immediate and delayed recall of the figure were used. Prose recall involved the recall of a short story (immediate and delayed, e.g. after approximately half an hour of further test administration).

1.3.10 Mental Flexibility (executive/frontal lobe function)

The Stroop test (Ternary et al, 1988) was included as a measure of mental flexibility and frontal lobe function. Performance on the verbal fluency task (FAS: Godowsky et al, 1967) was used to assess expressive language and frontal lobe function. For the first part, participants are required to list as many words beginning with the letters F, A and S and for the semantic part, participants are to list as many animals and household objects as they can. All tasks are to be completed in one minute. Trails B (Spree & Strauss, 1991) was also included to assess

frontal/executive function and this involves joining numbers and letters from lowest to highest and in alphabetical order.

1.3.11 Information Processing Speed Tests

AMIPB Information Processing Speed Tests (Coughlan & Hollows, 1985) were used in the test battery. Separate measures of mental and motor speed can be calculated from this test. Two scores for were used and these assessed how long it took participants to complete the task ('Task A' = total amount of correct responses within a time limit; 'Speed' = total number of digits crossed within a time limit). Trail Making A (Spree & Strauss, 1991) was also included in the battery which involved looking at scores to 1) join numbers form lowest to highest. This involved calculating the time taken in total to complete the task and the time (in seconds) is the overall score.

1.3.12 Psychological Measures

The Hospital Anxiety Depression Scale (HADS: Zigmond & Snaith, 1983) was administered to assess participants' level of anxiety and depression at the time of testing. This measure is designed to detect the presence and severity of anxiety and depression. It is a self-report measure and seven questions relating to anxiety are indicated by an 'A' while seven questions relating to depression are shown by a 'D'. Respondents are asked questions relating to their experiences of anxiety and depression over the last week. Each question has four responses (measured on a four point likert scale ranging from 0 (not at all) to 3 (nearly all of the time). Total scores are calculated for each of the subscales of anxiety and depression. Scores of 0-7 on each respective subscale are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'.

As outlined by Roberts, Bonnici, Mackinnon & Worcester (2001), reliability of the HADS is .98 for total score, .85 for anxiety subscale, and .80 for depression subscale. Test-retest reliability has produced coefficients over a two month period for the total score, anxiety subscale, and depression subscale (.79, .79, and .63 respectively). With regard to validity, Correlation coefficients between the HADS and Symptom Checklist 90 scale were .73 (anxiety subscale) and .67 (depression subscale (Bjelland I, Dahl AA, Haug TT, Neckelmann, 2002)

The Hospital Anxiety and Depression Scale is a well-known, reliable and valid instrument and is often used to assess the role of emotional factors in clinical practice. A brief questionnaire is provided, which takes between 5-10 minutes approximately to complete. Many studies have confirmed the validity of the Hospital Anxiety and Depression Scale in the setting for which it was designed. Other studies have shown it to be a useful instrument in other areas of clinical practice. Patients have no difficulty in understanding the reason for request to answer the questionnaire.

1.3.13 Procedure

Data from the neuropsychological examination were collected from patients attending the outpatient clinic of Hepatology, University College London Hospital between November 2006 and June 2007. All participants provided their signed consent and were given an information sheet explaining the purpose of the study (Appendix B).

The Neuropsychological tests were administered first. This battery was followed by the completion of psychological measures and brief clinical interview, asking about current occupational status, past occupational history, level of education

and gave the opportunity for each patient to elaborate on any aspect of current difficulties experienced.

1.3.14 Statistical Power

Finding comparable studies in order to calculate power calculations proved difficult. As was mentioned in the introduction, studies have utilised different methodologies, populations, psychological tests and control groups making direct comparisons problematic. However, studies by Pantiga et al (2001) found large effect sizes between cognitive function and cirrhotic/control participants on tasks of motor speed and mental flexibility, indicating that future studies would require a small sample size (6-8 patients with liver disease and 6-8 controls).

1.3.15 Data analysis and Statistical procedures

The data was corrected for age when required. On subtests of the WAIS-R, mean raw scores were converted to age adjusted scores by the use of the corresponding manual. On other tests within each domain studied, age was included as a covariate in statistical tests that analysed the data. The neuropsychological tests were grouped according to domain of psychological functioning.

1.4 Results

Table 4 gives the group characteristics of the study, in terms of age, Premorbid IQ and measures of anxiety and depression on the Hospital Anxiety and Depression Scale.

Table 4: Group Characteristics Between Patients and Controls

Group	Age	Premorbid IQ	HADS A	HADS D
Patients N = 27	54.81 (9.05)	109.74 (6.24)	6.81 (4.31)	5.33 (3.43)
Controls N = 22	45.59 (10.92)	111.27 (6.72)	4.45 (2.80)	1.95 (1.61)
	t(23)= 3.23*	t(23)=.82	t(23)=2.21**	t(23)=4.25**

*P<0.05;**P<0.01

Separate Independent t – tests were performed to test the difference between the two groups (patients vs. controls) on the variables of age, premorbid IQ, and measures of anxiety and depression as determined by the Hospital Anxiety and Depression Scale (HADS A and HADS D). These showed a significant difference between the groups in terms of Age, ($t(25) = 3.23$, $P<0.05$); HADS A ($t(25) = 2.21$, $P<0.01$) and HADS D ($t(25) = 4.25$, $P<0.01$). Patients were significantly older and showed greater depression and anxiety. [1]However, the means did not indicate clinically relevant levels of anxiety or depression. There were no significant differences between groups in terms of NART Premorbid IQ, ($t(25) = .82$, $P>0.05$)

1.4.1 Distribution of Variables

The distribution of the data was examined. The skew and kurtosis of two variables (the scores on Task A and Stroop) were over 2, so square root transformations were applied to both variables

1.4.2 Stage 1 – Liver disease patients and controls

Stage 1 of the data analysis involved investigating performances on neuropsychological test between patients and controls so as to test out the hypothesis that patients with liver disease will have poorer performances than the controls on neuropsychological tests.

The tests were clustered into related sub-groups for the purposes of conducting multiple analyses of variance so as to control for multiple testing without overly conservative thresholds of significance. These were WAIS-R subtests, test of motor speed, verbal and spatial memory and frontal/executive functioning. Anxiety and depression scores were entered as covariates in all analyses to control for the effects of these variables. Age was also entered for all but the WAIS-R subtests as these scores already take age into account.

Subtests of the WAIS-R

The group means and standard deviations between patients and controls on subtests of the WAIS-R – Block Design, Digit Span, Digit Symbol and Vocabulary - are presented in Table 5.

[1] Clinically relevant levels are as follows for adult (non-student) samples: means of 0-7 (normal); 8-10 (borderline); 11-21 (abnormal)

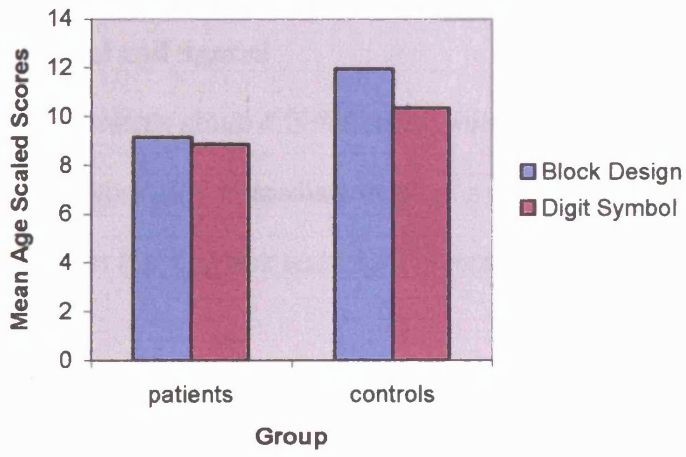
Table 5: Group Means on Subtests of the WAIS -R

	Test			
Group	Block Design	Digit Span	Digit Symbol	Vocabulary
Patients	9.14 (2.44)	10.22 (2.59)	8.85 (2.31)	11.51 (1.45)
Controls	11.95 (2.68)	10.86 (2.53)	10.36 (2.08)	12.04 (2.08)
	F (1,45) =14.77*	F(1,45) =1.84	F(1,45) = 4.61*	F(1,45) = 54

$P<0.05$

A MANCOVA was conducted to examine differences between the two groups (patients vs. controls), with the Anxiety and Depression variables (from the HADS) as covariates. This found significant differences overall ($F(1,48) = 4.04$, $P<0.05$) that were due to poorer performance in patients on the Block Design test and the Digit Symbol test. This is presented in Figure 1.

Figure 1: Group Scores on Block Design and Digit Symbol Tests



Motor Speed

Table 6 shows group differences on tests of motor functioning: Task A and Speed determined from AMIPB Information Processing Speed Tests

Table 6: Group Means on Tests of Motor Speed

	Test		
	Trail A	Task A	Speed
Group			
Patients	46.92 (13.21)	57.74 (7.46)	46.96 (7.28)
Controls	30.95 (6.41)	65.68 (13.44)	52.86 (9.80)
	F(1,45)= 10.76*	F(1,45) = 3.54	F(1,45) = 2.71

** P<0.01*

A MANCOVA was used to analyse the data, using Age, Depression and Anxiety as Covariates. This found significant differences between groups on tests of motor functioning, ($F(1,48) = 4.04$, $P<0.05$). Further analysis showed group differences on the Trail A test.

Memory – Verbal and Spatial

Table 7 presents group differences between patients and controls on tests of verbal memory: Story IR = immediate recall of a prose, Story DR = delayed recall of the prose; LL1-5 = list learning task and LLA6 = recall of items on list learning after a distraction

Table 7: Group Means on Tests of Verbal Memory

	Test			
Group	Story – IR	Story – DR	LL 1-5	LL A6
Patients	34.59 (9.37)	30.14 (9.18)	35.59 (10.00)	8.29 (2.64)
Controls	39.45 (12.07)	36.81 (11.29)	49.13 (7.55)	10.45 (2.87)
	F(1,45) = .16	F(1,45) = .28	F(1,45) = 15.72*	F(1,45) = 2.10

$P<0.05$

A MANCOVA was used to analyze the data further in terms of performances on verbal memory tasks, with Age, Depression and Anxiety as covariates.

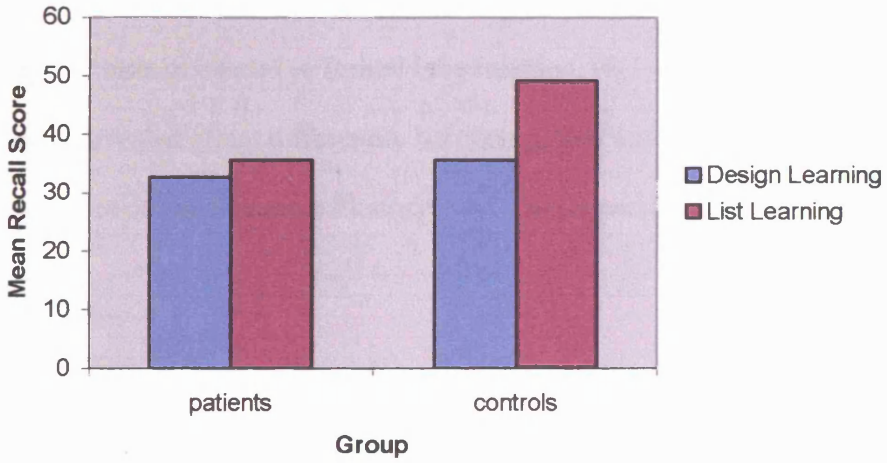
On tests of verbal memory, there was a significant difference on scores between groups overall ($F(1,48) = 3.83$, $P<0.05$) overall. Further analyses revealed a significant difference between groups on the List Learning task (LL1-5).

Table 8: Group Means on Tests of Spatial Memory

	Test			
	RCF – I	RCF – D	DL1-5	DA6
Group				
Patients	84.33 (7.66)	78.52 (7.55)	32.74 (4.19)	7.18 (1.11)
Controls	86.68 (14.99)	84.22 (15.31)	35.59 (6.41)	7.50 (1.68)

A MANCOVA was used to investigate the data further, with age, anxiety and depression as covariates. This found no significant results, ($F(1,48) = .66$, $P>0.05$). The scores between patients and controls on the List Learning Verbal task and Design Learning Spatial Tasks are presented in Figure 2.

Figure 2: Mean scores between patients and controls on tests of verbal memory: List Learning and Design Learning



Executive/Frontal Lobe function

Table 9 presents the scores between the patients and control groups on the tests of executive/frontal lobe function.

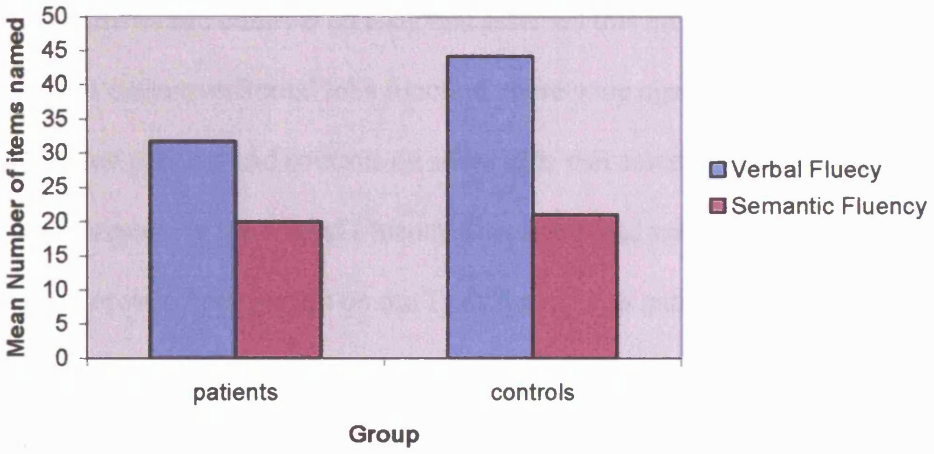
Table 9: Group Means on Tests of Executive/Frontal Lobe Function

	Test			
Group	Trail B	Stroop	VF	SF
Patients	89.03 (19.40)	101.18 (7.03)	31.70 (6.94)	20.00 (6.30)
Controls	65.95 (20.11)	106.86 (9.68)	44.13 (11.03)	21.00 (4.68)
	F(1,45) = 9.99*	F(1,45) = 1.84	F(1,45) = 11.65*	F(1,45) = .108

** P<0.01*

A MANCOVA was used to analyse the data further, using Age, Depression and Anxiety as a covariates. This found that there were significant differences between groups on tests of executive/frontal lobe function, ($F(1,48) = 4.67$, $P<0.05$). Further analysis revealed group differences between patient and controls on the Verbal Fluency Test but not on the Semantic Fluency Test. This is presented in Figure 3.

Figure 3: Mean scores between patients and controls on tests of frontal/executive functions



There were also significant differences between groups on the Trail B test, with patients having slower performances than controls.

1.4.3 Summary – Stage 1

Stage 1 involved comparing liver disease patients with a control group on performances on neuropsychological tests. On the domain of IQ functioning, there were significant differences between patients and controls on two tests that measured this - Block Design and Digit Symbol subtests. The patient group had significantly poorer performances on both and their age adjusted scaled scores were lower. There were no differences between patients and controls on other subtests of IQ functioning, namely Vocabulary and Digit Span, although on both tests patients again had lower age adjusted scaled scores.

On the domain of motor speed, significant differences between patients and controls were found on one test that measured this area of functioning - the Trail A test. Patients took longer to complete the task. There were also significant differences

between patients and controls on verbal memory – the patients recalled fewer items on the List Learning task than controls. On spatial memory, no significant differences were found between patients and controls on tests that assessed this area of functioning.

Finally, on executive/frontal lobe function, there were again significant differences between patients and controls on some tests that assessed this area. Patients had poorer performance on the Verbal Fluency Test compared with controls. There were also differences between both groups on the Trail B test, with patients having slower reaction times.

The results therefore support the hypothesis that patients with liver disease have greater deficits in areas of cognitive functioning. They had poorer performances than controls on a wide range of neuropsychological tests, although a pattern of global cognitive deterioration was not observed.

1.4.4 Stage 2 – Patients with liver disease

The next stage of the analysis involved investigating whether greater cognitve deficits were observed in those patients with more severe forms of liver disease and whether performance on neuropsychological tests was influenced by severity of disease, as determined by the Child Pugh scores. Multiple analyses of variance comparing the three groups were conducted using the same grouping of variables as used in Stage 1.

Table 10 presents demographic information, premorbid IQ and information regarding severity of mood disorder amongst patients with different degrees of liver disease (determined by Child Pugh stage).

Table 10: Group Characteristics Between Patients

Group	Age	Premorbid IQ	HADS A	HADS D
A N = 10	53.80 (9.62)	110.90 (6.87)	8.90 (4.04)	6.00 (2.30)
B N = 8	54.12 (10.54)	109.37 (2.61)	5.50 (3.89)	5.87 (5.16)
C N = 9	56.55 (7.73)	108.77 (8.05)	5.66 (4.50)	4.11 (2.52)

Separate one-way ANOVAs were performed to investigate differences between liver disease groups in terms of Age, NART IQ, HADS A and HADS D. No significant differences on any of the above variables were observed, although there was a non-significant tendency for Group A to report more depressed symptomatology.

Subtests of the WAIS-R

Table 11 presents differences between liver patients on the subtests of the WAIS-R - Digit Span, Vocabulary, Block Design and Digit Symbol; Groups A, B and C determined by Child Pugh score.

Table 11: Group Means on Tests of WAIS-R

	Test			
Group	Digit Span	Vocabulary	Block Design	Digit Symbol
A	11.50 (2.83)	11.80 (1.75)	10.50 (2.59)	9.60 (2.01)
B	10.12 (2.03)	10.87 (1.24)	9.75 (2.12)	10.25 (1.90)
C	8.88 (2.22)	11.77 (1.20)	7.11 (1.78)	6.77 (1.48)
	F(1,24) = 7.24	F(1,24) = 1.13	F(1,24) = 7.24*	F(1,24) = 9.05*

$P<0.01$

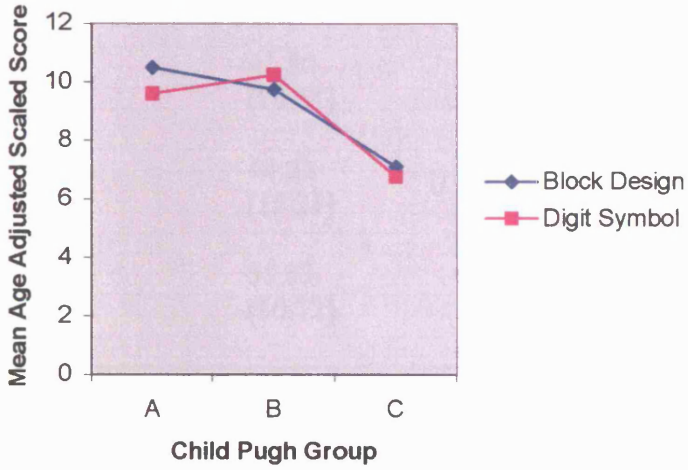
A MANOVA was performed on the data above to investigate group differences on the above tests. This showed that there were significant differences between patients on these tests, ($F(1,27) = 3.87$, $P<0.05$). Further analyses revealed group differences on Block Design and Digit Symbol.

Independent samples t-tests were performed and the Bonferonni adjustment was set at 0.012. A significant difference was found between Groups A and C on scores of Block Design, ($t(11) = 3.96$, $P<0.01$) and on scores of Digit Symbol, ($t(11) = 3.50$, $P<0.01$).

Independent samples t tests also showed there were significant differences between Groups B and C on scores of Block Design, ($t(11) = 3.48$, $P<0.01$) and Digit Symbol, ($t(11) = 4.21$, $P<0.01$).

This is presented in Figure 4

Figure 4: Mean scores on subtests of WAIS-R: Block Design and Digit Symbol between Groups A, B and C



Motor Speed

Table 12 presents differences between liver disease patients on tests of Motor Speed

Table 12: Group Means on Tests of Motor Speed

		Test	
Group	Trail A	Task A	Speed
A	41.50 (10.61)	61.90 (4.22)	48.10 (6.13)
B	44.25 (15.21)	57.50 (9.42)	49.12 (6.72)
C	55.33 (10.72)	53.33 (6.30)	43.77 (8.54)

A MANCOVA was used to investigate the data further. This found no significant differences between groups on tests of motor speed, ($F(1,27) = 1.88$, $P>0.05$).

Memory – Verbal and Spatial

Table 13 presents the group means on tests of verbal memory.

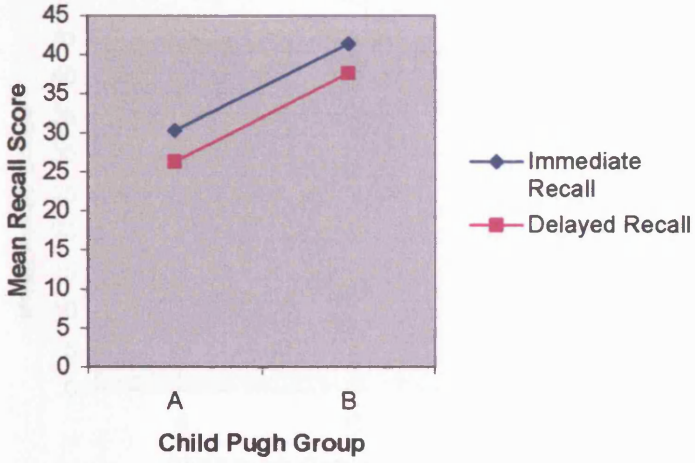
Table 13: Group Means on Tests of Verbal Memory

	Test			
Group	Story – IR	Story – DR	LL 1-5	LL A6
A	30.30 (10.85)	26.30 (10.87)	40.50 (7.39)	8.20 (3.04)
B	41.37 (12.07)	37.62 (11.29)	35.12 (7.55)	9.25 (2.87)
C	33.33 (8.55)	27.77 (7.04)	30.55 (10.71)	7.55 (2.29)
	F(1,27) = 3.95*	F(1,27) = 5.01*	F(1,27) = 2.64	F(1,27) = .87

$P<0.05$

Separate MANCOVA's were used to analyze group differences on tests of verbal memory and a significant difference was found between groups, ($F(1,27) = 2.53$, $P<0.05$). Closer analyses revealed differences between groups on immediate recall and delayed recall of a story. Independent t tests were used to investigate differences further and the Bonferonni adjustment was calculated at 0.012. These showed Group A had significantly worse recall scores than Group B on both immediate and delayed recall of a short story ($t(11) = 3.06$) and ($t(11) = 3.10$, $P<0.012$) respectively. This is shown in Figure 5.

Figure 5: Mean delayed and immediate recall scores: Group A and B



Independent t tests also showed that Group C had significantly worse scores on delayed recall of a story compared with Group B, ($t(11) = 3.57$, $P<0.012$) but not on immediate recall of a story, $t(11) = 2.62$, $P>0.012$. This is shown in Figure 6

Figure 6: Mean immediate and delayed recall of story: Group B and C

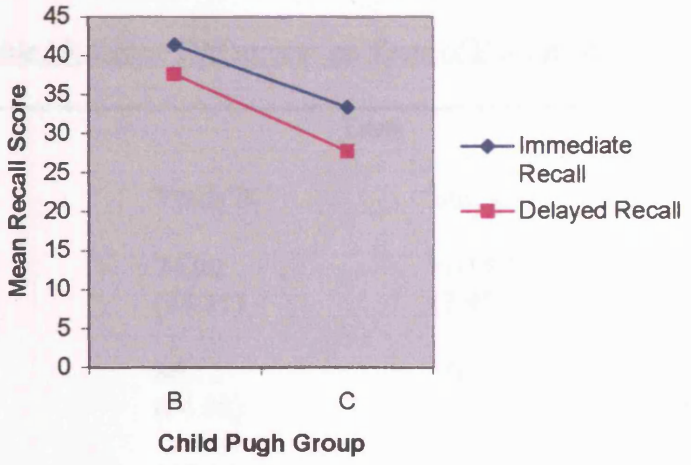


Table 14 presents group differences on tests of spatial memory

Table 14: Group Differences on Tests of Spatial Memory

	Test			
	RCF – I	RCF – D	DL1-5	DA6
Group				
A	88.20 (7.98)	80.75 (8.53)	35.30 (4.39)	7.10 (1.19)
B	85.00 (4.53)	79.25 (6.51)	31.37 (3.58)	7.00 (1.30)
C	79.44 (7.43)	75.88 (7.54)	31.11 (3.33)	7.44 (1.88)

No significant differences between groups were found on tests of spatial memory, ($F(1,27) = 1.51$, $P>0.05$)

Executive/Frontal Lobe Function

Table 15 presents group differences on tests of executive/frontal lobe function

Table 15: Group Differences on Tests of Executive/Frontal Lobe Function

	Tests			
Group	Trails B	Stroop	VFT	SFT
A	74.90 (13.31)	102.80 (7.95)	33.50 (7.21)	21.11 (4.85)
B	86.12 (14.98)	102.25 (5.62)	32.62 (7.57)	19.62 (5.95)
C	107.33 (13.87)	98.44 (7.03)	28.88 (5.84)	19.22 (8.21)
	F(1,27) = 11.62*	F(1,27) = .81	F(1,27) = 1.18	F(1,27) = .208

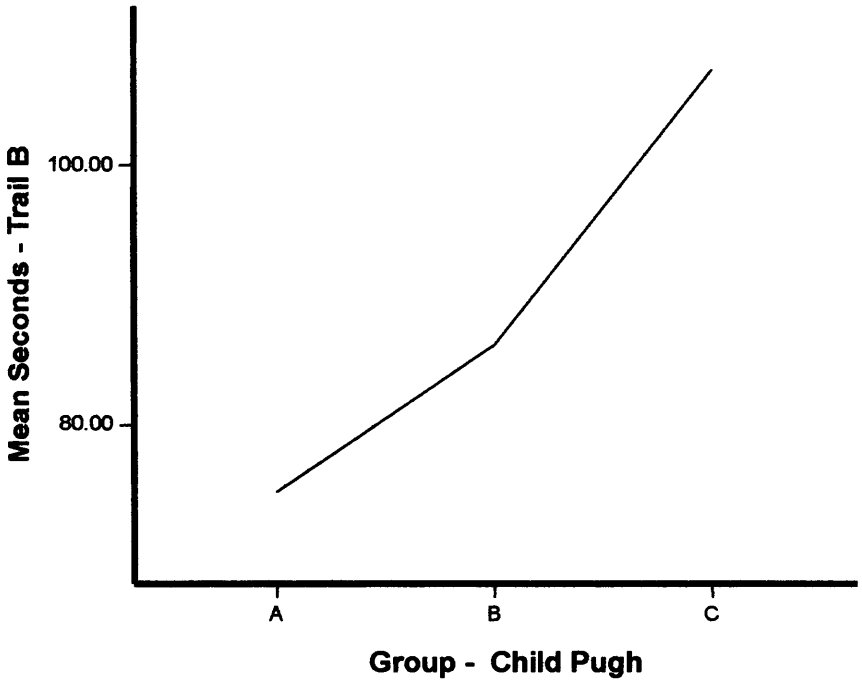
**P<0.01*

A MANCOVA found significant differences between groups on these tests, (F (1,27) = 2.23, P<0.05). Further analyses showed there were significant differences between groups on the Trails B test.

Independent t tests were performed to investigate group differences on the Trails B scores. These showed that Group C had significantly slower performances than Group A, (t (11) = .51, P<0.001) and Group B, (t(11) = .301, P<0.01). Scores were not significantly different between Group A and B, (t(11) = 1.68, P>0.05).

This is illustrated in Figure 7

Figure 7: Mean RT (seconds) on Trail B Test between Groups A, B and C.



1.4.5 Summary – Stage 2

Stage 2 of the data analysis compared cognitive functioning in different liver disease groups, as determined by the Child Pugh Score.

On domains of IQ functioning, differences were observed. Group C had worse performances than Group A on the Block Design and Digit Symbol tasks. The findings also showed that performances were significantly worse in Group C on both of these tests than Group B. On tests of motor speed, Group C had worse performance on all three tests although the difference did not reach significance.

On domains of verbal memory, further differences were observed between liver disease groups. Group C had significantly worse performance than Group B on recalling a short prose after a delay. Additionally, Group A had poorer immediate and delayed

recall scores compared with Group B. No significant differences were observed between liver disease groups on tests of spatial memory.

Finally on executive/frontal lobe function, differences were observed. Reaction times were significantly slower in Group C than Group B and A on the Trails B test.

1.4.6 Conclusion

The results from this study are mixed. Although they support both of the hypothesis tested, they show that there is also some variation. Therefore, there does not appear to be a global deterioration in cognitive deficits in liver disease (as measured by the neuropsychological tests used in this study).

1.5 Discussion

1.5.1 Overview

The findings support the hypothesis of deficits in cognitive functioning in patients with liver disease. Compared with controls, the liver disease patients had poorer performances on neuropsychological tests. The findings also support the hypothesis of greater deficits in those with more severe cases of liver disease. Those with more severe stages of liver disease (Child Pugh C) had worse performances on tests measuring cognitive domains than those with less severe liver functioning (Child Pugh A). Furthermore, the profile of deficit is similar to that seen between healthy control subjects and liver patients. The one anomaly was the observation that Group A had poorer performances than Group B on some domains (verbal memory) indicating memory deficits were experienced by those with better liver functioning.

In Stage 1 of the analysis, patients and controls were compared on neuropsychological performances on tests that measured cognitive domains and areas of functioning. General intellectual ability was relatively well preserved in the patient

group. However, the results suggest they had greater impairment on most of the areas of functioning investigated; IQ functioning, motor functioning, verbal memory and executive/frontal lobe functioning. Their performances on tests that measured each domain were worse in all of these areas.

In Stage 2 of the data analysis, patients with different severity of liver disease were investigated with regard to the same domains of cognitive functioning. The findings showed that those with worse stages of liver disease (the Child Pugh C Group) had greater deficits in some areas compared with those patients with less severe stages of liver disease (the Child Pugh A Group). Therefore, worse performances on various neuropsychological tests was observed when liver function was estimated to be worse and more severe; performances were shown to be poorer on domains of IQ functioning and some executive/frontal lobe tasks.

The results from the current study are therefore mixed. The first and second hypotheses were supported although there was not a global deterioration of deficits in patients with liver disease. Stage 1 and 2 found that performances by 1) liver disease patients and 2) more severe stages of liver disease were not consistently poor, i.e. on all neuropsychological tests. An unexpected anomaly however, was that patients with better liver functioning in Group A had greater deficits in verbal memory functioning than those patients with worse liver functioning in Group B.

1.5.2 Comparison with previous research

The results from the current study tie in with previous studies that have found poorer performances on cognitive domains between liver disease patients and matched controls. Pantiga, Rodrigo, Cuesta, Lopez and Arias (2001) found that cirrhotic patients showed a degree of mental impairment in functions studied (memory and immediate

recall, motor processing and mental flexibility and general reasoning/non-verbal intelligence). They argued that severity of the deficit was related to the degree of hepatic dysfunction. The current study partially supports this finding although it demonstrated deficits are not consistently observed in worse stages of liver disease. Those with better liver functioning demonstrated more impairment in verbal memory functioning. The current study differed also in that general reasoning ability was not directly studied.

Mechtcheriakov, Graziadei, Mattedi, Bodner, Kugener, Hinterhuber, Marksteiner and Vogel (2004) also found significant differences between patients with liver disease and controls on domains of motor functioning, executive functioning and memory. The current study therefore supports their work and reflects their findings.

Similar findings have been obtained by Weissenborn, Heidenreich, Giewekemeyer, Ruckert and Hecker (2003) who observed differences between patients with minimal hepatic encephalopathy and controls in domains of memory, attention and non-verbal intelligence. However, they did not find consistent differences on memory functioning and spatial memory was preserved in patients with liver disease. This supports the findings from the present study in that no group differences on domains of spatial memory were observed in either Stage 1 or Stage 2 of the data analysis.

The most common patterns of cognitive deficit in patients with liver disease have therefore been observed in psychomotor and executive functioning. Other areas of ability are less well understood, for example patients have shown less prominent deficits in other neuropsychological domains, such as memory and verbal ability. Memory functioning has not been consistently demonstrated in patients with liver disease and some researchers have argued that deficits observed are primarily in attention and visual perception, rather than memory. The findings suggest that it is not the severity of liver

disease that is associated with deficits in all areas of cognitive functioning and that those with less severe forms of liver disease can have deficits in verbal memory compared with those with more advanced liver disease.

In the present study, liver disease patients had worse performances on the domain of verbal memory than controls (as demonstrated by their scores on the list learning task). Spatial memory was not significantly worse in liver disease patients than controls, however. This has been observed in other studies although findings with regard to spatial memory functioning in liver disease are mixed.

Verbal skills appear to remain intact in patients with liver disease and in the current study, patients did not perform worse than controls on verbal IQ, as reflected by the Vocabulary subtest of the WAIS-R. This has also been observed in other studies. For example, McCrea et al (1999) observed a selective dysfunction of attention and motor skills in cirrhotics in the absence of any impairment in general intellect, memory, language or visuo-spatial skills.

The findings do not suggest a global decline of cognitive functioning in liver disease. For example, it is apparent that significant deficits were not found between patients and controls on all tests used to measure motor processing. Although patients had worse performances on all tests that measure this domain, the differences did not emerge as significant on all tests. Likewise, a consistent pattern of deficits in executive/frontal lobe functioning was not observed in liver disease patients compared with controls.

The study differed from previous research in that few studies have directly compared performances between patients with different stages of liver disease, with severity determined by Child Pugh scores. Most studies have looked at performances

between liver disease patients and controls. Pantiga et al (2001) found that patients with Child Pugh stage C had deficits in IQ functioning than those with less severe stages of liver disease. Pantiga et al also found that patients with Child Pugh stage C had more impairment on frontal lobe/executive functioning skills than those with a Child Pugh score of A. The present study partially supports this finding in those patients in the Child Pugh C group had worse performances on one test that measured this domain (Trails B) compared with those patients in the Child Pugh B and A group. However, their performances on other tests did not differ significantly.

Another observation from the current research was that the liver patients had significantly higher means on measures of anxiety and depression the controls (although scores were not clinically relevant). The psychological implications associated with liver disease have been studied to a lesser extent than cognitive deficits and could benefit from further research.

Severity of liver disease has been found to have effects on self-reported measures of well-being. For example, Park, Park, Kim, Park, Hyan, Yun, Jo, Tak, Kweon, Kim, Choi & Park (2003) found less severity of liver disease is associated with poorer scores on measures of mood. In the current study, those patients in the Child Pugh A group (less severe liver disease) had slightly higher means on the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) than those in the Child Pugh stage C group (more severe liver disease), although this did not reach clinical levels or significance and no conclusions can be drawn.

1.5.3 Emotional Factors

The present study found that differences between performances on neuropsychological tests were observed despite controlling for effects of anxiety and depression. Although the liver disease patients had higher means on measures of anxiety and depression than controls, these were not in the clinically relevant range. Additionally, statistical methods controlled for the effects of mood and the observed differences on neuropsychological tests between patients and controls cannot be attributed to effects of depression or anxiety. Therefore, this study found little evidence to substantiate the view that deficits were secondary to psychological distress.

Opinions differ as to the nature, extent and aetiology of cognitive impairment in depressed and anxious patients. There may be other factors and variables associated with both mood states that may impact on functioning and performances (i.e. associated with quality of life, effort made and fatigue). It is also difficult to control for other potentially confounding variables such as medication.

Additionally, although some investigators have found differences between control subjects and depressed patients on certain memory (prose recall, list learning, design learning) and information-processing speed tasks (Watts, 1996) mood disorder is associated with a lesser degree of impairment than organic brain damage (Watts, 1996). Further still, differences in task performance between control subjects and those who are depressed have been shown to be non-existent or very small which has led some researchers to suggest that poor performance may be secondary to lack of motivation. Lezak (2004) for example found that depressed patients frequently show errors of omission or give 'don't know' responses, suggesting a lack of effort.

It can be suggested that the differences seen in the current study could be attributed to effects of state anxiety as opposed to higher but non-clinical levels of trait anxiety. A measure of state anxiety was not taken and patients could have been more temporarily anxious than control participants. Trait anxiety has been considered to have little effect on performance but state anxiety has opposing effects on high and low ability participants. It has been considered to enhance performance of high ability subjects but has the opposite effect on low ability subjects. In the current study, however, all participants were matched on premorbid IQ.

Physical fatigue, memory and concentration problems are reported by many liver disease patients. Chronic fatigue syndrome is the term usually applied to people with a history of unexplained fatigue coupled with other physical problems. It also includes people who are suffering from anxiety or depression and those with medical conditions such as multiple sclerosis. Although there is no specific abnormality associated with CFS, psychological disorder is found in approximately 75% of CFS patients. Around 50-70% of CFS patients complain of considerable difficulties with memory and concentration and these difficulties are often associated in occupational difficulties (McDonald, Cope & David, 1993). It is unknown how many patients in the current study were experiencing CFS.

Therefore, the current study suggests effects on neuropsychological performances cannot be attributed to psychological factors, such as anxiety or depression. However, this does not rule out such factors entirely, as effort and motivation might have been poorer in the patient group, or effects might have been a result of fatigue. For example, tests that require sustained attention and concentration (tests which measure memory functioning) or construction skills (some subtests of the

wais, i.e. block design) or movement/psychomotor skills (tests such as Trails A) might be subject to fatigue.

Anxiety has been established in liver disease patients, particularly with regards to before and after liver transplantation (Moore, Burrows & Hardy, 2006). Patients with end-stage liver disease due to hepatitis C have also been found to be more depressed than other liver disease patients (Singh, Gayowski, Wagener & Marino, 1997). Psychological distress has also been observed in chronic, nonalcoholic, uncomplicated liver disease (Davis, De-Nour, Shouval & Melmed, 1998).

Collis & Lloyd (1992) discussed the effects of liver disease on mental health and explained how this topic has been relatively neglected in the literature. They discussed the psychological consequences of specific liver disorders including sexual function, mental disturbance, effects of childhood liver disease, psychiatric aspects of liver transplantation and the use of psychotropic drugs in patients with hepatic dysfunction. This implies there are a number of clinical implications and a role for psychological input with regards to the effective treatment and care strategies of patients with liver disease.

1.5.4 Implications of Cognitive Deficits

Most of the patients in the research reported having some difficulties with concentration and/or attention and although deficits were not consistently demonstrated on all aspects of functioning, some felt that they had experienced problems. Various implications arise from cognitive deficits. Poor psychomotor speed can lead to general slowing of reaction times and skills needed to make quick responses. This could impact on skills such as driving, operating machinery or attempting to perform various tasks at once. This could make everyday tasks, such as driving, difficult.

As outlined earlier, Schomerus et al (2004) concluded that cerebral dysfunction in MHE had a major impact on patient's daily living and concluded 60% of cirrhotic patients without clinical signs of HE were considered unfit to drive and in 25% driving capacity was questionable.

Additionally, Bajaj, Hafeezullah, Hoffman & Saeian (2006) discussed how MHE patients have impairment on driving tests although they explained how it remains unclear whether this impairment is restricted to testing or is associated with an increased risk of traffic violations. They performed a study looking at 200 cirrhotics without overt HE and 100 age matched controls who were investigated with regards to a driving history and behaviour questionnaire inquiring about demographics, alcohol/illegal drug use and motor vehicle accidents and traffic violations within 5 years. Their results showed cirrhotics have a higher reported occurrence of both compared to controls. They also found that self-assessment of driving behaviour is not accurate in this population.

Poor memory would also impact on general functioning, especially verbal memory that relates to information heard and memory for words as opposed to memory for pictures. Therefore, deficits with verbal memory would manifest itself by impairments with remembering certain types of information, such as instructions or work-related activities.

1.5.5 Further research and implications

The literature on MHE has outlined how patients often describe mild cognitive alterations in this condition. It can be suggested that in some instances the changes are too mild to be acknowledged by the individual and can only be identified through objective tests. Or, alternatively, patients might feel they are lacking in concentration or have memory problems, yet objective tests might not demonstrate any deficits.

Therefore, further research could also look into whether there are any discrepancies between self report and objective measures between patients with different severity of liver disease.

Further research could also look into whether a specific 'profile' of cognitive deficits is characteristic of MHE. Although poor motor speed/executive functioning has been consistently demonstrated, other deficits could characterise this syndrome, such as memory impairments. The current study suggested verbal memory is associated with deficits in early stages of liver disease yet spatial memory is preserved. Therefore, further research could investigate this in order to see whether particular patterns of deficit emerge, such as in Attention Deficit Hyperactivity Disorder and Asperger's.

Future research could help to establish features (i.e. cognitive deficits/the association between liver disease and mood) that are characteristic of various stages of liver disease. This could help identify those patients who display signs of minimal hepatic encephalopathy or early stages of liver disease and help establish 'predictors' of future problems. This would enable early intervention and treatment strategies that would involve medical care and support of such individuals to reduce their symptoms, progression of liver disease and any further distress experienced.

Clinical considerations also emerge from this research. The types of deficits observed would clearly impact on a person's life and ability to perform everyday activities. Reduced motor speed would manifest itself by a general 'slowing down' and an increase in time spent performing tasks. This could make simple tasks, such as climbing stairs or crossing a road, difficult and could ultimately affect a person's safety. As outlined earlier, this could also impact of driving ability and increase the risk of accidents.

Additionally, deficits in executive functioning would also have a number of clinical implications. Executive functioning can be described as the brain's ability to absorb and interpret information and make decisions based upon such information. Deficits in this would include inappropriate interpretations, poor decision-making, loose associations, (thoughts loosely associated with one another), attention inhibition and impulsivity, problems shifting or switching attention, literal thinking and problem solving. It would also affect the ability to plan events successfully based on a set of instructions and devising various strategies, i.e. that would enable successful completion of a task.

Memory problems, specifically verbal memory difficulties would lead to increased forgetfulness of verbal material or for information heard. This would again impact on an individual's everyday life as they would find it more and more difficult to remember instructions or information that they had been told. This would lead to difficulties keeping appointments or making arrangements. This could also affect personal safety, i.e., when using electrical appliances and remembering instructions for use. Therefore, psychological input could involve helping patients manage and control these difficulties and helping them to develop strategies to compensate for their deficits. For example, assisting with the development of strategies to aid memory (i.e. 'post it's', diaries). Additionally, those with more severe stages of liver disease could benefit from extra support with performing everyday activities.

All of the above would have occupational consequences and it may be more difficult to keep a job. As outlined earlier, this was observed by Schomerus et al (2003), who found 73% of cirrhotics who were blue collar workers had impaired earning capacity in the presence of minimal HE; 50% of the white collar workers were fit for

work, even in the presence of minimal HE due to the preservation of verbal abilities in this condition.

Further still, while 80% of white collar workers suffering from cirrhosis were considered fit for work, only 40% of blue-collar workers met such criteria. This illustrates the importance of a significant impairment of motor performance in minimal HE where verbal abilities appear unaffected. In relation to this, reduced work-related activities could lead to periods of unemployment, which could cause periods of anxiety (i.e. finance related) and depression (i.e. inactivity).

As quality of life has been reported as being poor in patients with liver disease, the implications in terms of mental health is also another clinical implication. Park, Park, Kim, Park, Hyan, Yun, Jo, Tak, Kweon, Kim, Choi and Park (2003) found quality of life scores were significantly lower in liver disease patients than controls and the differences were greater on measures of mental as opposed to physical health. Additionally, when patient group was classified as Child A, B or C according to modified Child Pugh classification, severe liver disease was associated with lower quality of life scores. This suggests that quality of life decreases as liver disease worsens and could be correlated with cognitive deficits. Therefore, determining a role for future psychological input due to poor outcome measures on mental domains is a consideration. For example, this might be most important for those patients in the severe stages of liver disease who have been found to report worse quality of life than those patients at less severe stages of liver disease.

1.5.6 Limitations of the research

The major weakness of the present study is the sample size. A total of 27 patients were included in the current study, making comparisons between patients and controls

sufficient. However, it is more difficult to make generalizations about the findings from the liver disease patients as numbers in each group were relatively smaller. The largest group was the Child Pugh A group, which contained 10 patients. However, Group B had 8 patients and Group C 9 patients. Therefore, it is important to bear this in mind when attempting to make generalizations about the wider liver disease population.

Another limitation is that only one psychological measure was included in the present study and the research would have been improved if another measure was included, i.e. of general wellbeing. This might have shed light on why the patients in the study reported higher anxiety and depression scores, (although these were not clinically significant), than the control group. A wider understanding of their experiences might have been derived.

A further weakness is that patients with liver disease of different aetiologies were included and it is therefore not possible to make conclusions about cognitive deficits observed in specific types of liver disease. However, this has been acknowledged in the literature and further work will help establish whether there are precise 'patterns' of cognitive deficits associated in various types of liver disease.

The current study did not include any of the tests that have been used in some clinical and research settings for diagnostic purposes with regards to minimal hepatic encephalopathy. Patients did not participate if they were thought to have overt signs of hepatic encephalopathy. However, due to the complexities associated with the measurement of minimal hepatic encephalopathy, no definite conclusions about cognitive impairments in this syndrome can be drawn although findings can be considered in further research into this syndrome. A further elaboration of findings, with ideas for future research and clinical implications is given in section 3.

1.5.7 Conclusion

The results from the current study therefore suggest possible deficits in liver disease in terms of psychomotor speed and frontal/executive functioning. They also suggest that different patterns of deficits emerge in different severity/stages of liver disease. The research has therefore provided a basis that can be followed up in future studies in order to understand the patterns and nature of deficits in patients with liver disease.

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Part 3:

Critical Appraisal

1.1 Personal reflection.

The research reported in this thesis has been both an interesting and challenging experience. At times the process was rewarding, at others very frustrating. Research is central to the role of a clinical psychologist as it enables further knowledge of psychological problems. The current research constituted a complex study into a medical condition. It involved considering studies from different areas and incorporating both the medical model with psychological theories. Although this was an interesting and innovative way of understanding the impacts of a medical condition, the approach did have its challenges.

Liver disease is a complex physical illness and the prevalence is increasing. The incidence of excessive or 'binge drinking' is also increasing. The long time implications of this are unknown but substantial research has shown increased alcohol intake increases chances of developing liver disease, which is associated with cognitive, behavioural and physical problems. Also, the prevalence of mental illness in liver disease has been questioned and the impact on quality of life, ability to perform activities in general living, maintain employment/social life, capacity to manage finances, drive and maintain self-care, etc, is poorly understood.

Collis and Lloyd (1992) outlined how the effects of liver disease on mental health are relatively unknown and that this is a topic that been neglected in recent psychiatric literature. In their review, they outline how further work should address the psychological consequences of specific liver disorders, including sexual function, the relationship between alcohol and hepatic disorder in causing mental disturbance, the effects of childhood liver disease, psychiatric aspects of liver transplantation and the use of psychotropic drugs in patients with hepatic dysfunction.

The current study involved working alongside other health professionals, something that is also central to the role of a clinical psychologist. This provides an insight into the many different aspects of an individual's problem. The patients whom participated in the research were attending a specialised hepatology clinic as part of their medical care. The hypothesis that was addressed was that such patients would have cognitive deficits as demonstrated on neuropsychological tests. Previous work had shown patients complained of cognitive alterations and reduced work-related activities. However, due to lack of research, the precise spectrum of deficits and their cause remained unknown.

1.2 Why choose a Neuropsychological study?

The study of the various brain regions and how they are involved in cognition is a very interesting area of psychology and can be used to understand both normal and impaired processes. The reasons for choosing a research study can be both influenced by practicalities (i.e. constraints of work/placement settings) and personal (i.e. interests and motivation). As the research reported was not influenced by placement constraints, the main reasons for choosing the study were personal interest.

Before starting the Doctorate in Clinical Psychology in 2004, I had completed a Ph.D. in attentional biases in anxiety. Therefore, I had a keen interest in psychological factors in mood states, how particular thought styles and patterns develop and how they are maintained. Although I enjoyed the Ph.D. experience, the research mainly involved studying undergraduates and I found that any findings were difficult to generalise to the general population. I also developed an interest in researching clinical populations as I personally found this more fulfilling.

Although I would have liked to extend the findings from my Ph.D. to clinical populations as part of the research whilst on the course, this was not possible to do practically. Therefore, I decided to follow a research project in another area that I was very interested in which was Neuropsychology. I had enjoyed this in my undergraduate degree although I had little experience of neuropsychological testing. I also was very keen to further my experience in this area and thought the research would provide a unique opportunity to discover whether it is an area I would like to work in upon finishing the doctorate at UCL.

At the time of choosing a suitable project for the thesis, it became apparent that there was an opportunity to work in collaboration with the Institute of Hepatology (IoH), University College London. There were a few possible projects to follow, so a meeting followed with the consultant of Hepatology and his Research Fellow. At this stage, the Research Fellow was very keen to have some extra psychological input on a study he was carrying out looking at the effects of probiotics. However, this study sounded much grounded in the medical model and I decided against becoming involved. I was given some references from both my internal and potential external supervisors (the Hepatology consultant at the IoH).

Choosing a viable and realistic research project that was suitable for a trainee clinical psychologist proved difficult; the references were rather complex and contained a lot of medical terminology. At times, it felt rather overwhelming and the literature extremely complex. Consequently, it could feel impossible to conduct a project that would be suitable for a DClinPsych project – some of the ideas sounded as if they were beyond the scope of a suitable project because of time and resources that would be required to undertake the work.

I eventually decided on investigating the characterisation of cognitive deficits in liver disease. As outlined above, I was keen to further my experience of neuropsychological testing and found this option the most realistic.

1.3 Planning of the Research

One of the biggest challenges was actually coming up with some clear aims and objectives for the study. At the early stages of this process I often felt rather unsure of any specific aims and rather overwhelmed with the literature and the medical terminology.

Minimal Hepatic Encephalopathy is still a relatively new phenomenon and little is understood about the psychological effects on people with early stages of liver disease (Pantiga et al, 2001). It is understood of manifesting itself by subtle cognitive changes and reported cognitive alterations (Matorrozi et al 2007), with reduced work related activities. Although there appeared to be some scope for psychological input, it was not altogether clear about what this input could be. There had to be a justification for performing neuropsychological tests on people who were in poor health and comparing them to a control group and it took some time to arrive at this, as well as a suitable study.

Subsequently, the initial proposal was heavily questioned and required major amendments. There was some confusion about aims, methodology and design. The proposal was generally considered to be vague and unspecific, which probably reflected the complexities of the area and the lack of clarity felt. Therefore, the proposal was revised and upon further reading of possible effects of MHE, it was decided to use the increased ammonia hypothesis as a basis for making specific hypothesis about what was expected to happen in the research, i.e. as the severity of liver disease increases possibly

due to increased ammonia levels, cognitive deficits would become increasingly impaired.

In retrospect, it would have been useful to have had more time to read and understand the literature but due to tight deadlines this was not possible. Fully absorbing the literature in order to arrive at a suitable and appropriate study was time consuming and the study could be considered a little ambitious for a trainee, given that a design was not already available. It would have also been useful to have had a series of meetings scheduled in between my internal and external supervisors as at times it felt difficult juggling the demands and requirements/points of view from different directions.

Once the revised proposal was approved, it was necessary to think about ethical approval and constructing participant information sheets. It was also necessary to consider a test protocol and familiarize myself with neuropsychological tests. All stages, again, were associated with many challenges and it took some time to address. Consequently, I felt rather behind and my general progress was questioned regularly.

1.4 Methodological issues

Once a general aim with specific hypothesis had been achieved, it was necessary to think about the design and test protocol, as outlined above. The design of the study appeared quite straightforward and the test protocol involved deciding on a test battery to include in the study. All tests used were well validated, researched and standardised. Having little experience of neuropsychological testing, this part was decided on by my internal UCL supervisor and decisions about which tests were reached after reviewing other studies that had found cognitive deficits in early stages of liver disease. A full, comprehensive test battery was decided on in order to consider the full spectrum of possible deficits in this patient group.

There were a number of further, ethical considerations to consider in the study. One was the testing of patients who were clearly unwell, especially those in the 'later' stages of severity of Liver Disease as measured by the Child Pugh C group. Therefore, informed consent was always given and the full purpose of the study explained. Patients were also compensated for their time. However, as the study progressed it was clear that most patients were happy to help out and felt that they were giving something back to the doctors who had helped them. They felt that they wanted to be involved in research that would further knowledge and understanding about their condition.

Although most patients were keen to oblige, and understood about having little direct benefit by participating in the study, one or two patients were clearly confused about the reasons they were asked. For example, one worried about whether or not the study was identifying patients with dementia. Other complications included lack of understanding about my role and one patient appeared frustrated that I did not have a wide understanding of his condition and had not read his file. Therefore, these could be issues that might lead to questions about the ethical stance of using patients who were in poor health to participate in a study such as this.

Patient recruitment was another challenge associated with the research. A copy of the research proposal was sent to my external supervisor at the IoH/UCLH and his registrar. This included inclusion/exclusion criteria with regard to the suitability of patients who could participate. The registrar was to send names and hospital numbers of such patients and it was my duty to contact the secretary for contact details. However, it soon became apparent that some patients had been selected who were not suitable for the study. For example, some had ongoing alcohol use and a couple were clearly

intoxicated. Further still, patients would at times not attend nor cancel their appointments.

Further challenges with regard to recruitment included having to contact the secretary at the clinic for contact details of all the patients I was sent (the process could take up to two weeks for each patient) and having very 'dry' periods when no patients were sent. The registrar left half way through the study and other members of the medical team at UCH were left with the responsibility to send patients to me for the study. However, this involved having to constantly 'chase' the medics involved which could be difficult to implement.

Moreover, further difficulties were encountered with regard to the actual testing of patients. There was not always a room available at the liver clinic (where I would meet patients) so one needed to be booked through the reservations system. The room offered could be at one of numerous locations and sometimes it involved a short walk from the hospital. At times, patients would turn up with mobility problems and this was difficult. At other times, patients would simply not show up or cancel their appointments, or turn up with partners who were very keen to sit in on the sessions.

Further still, as I required the patients Child Pugh scores in order to determine which group each patient would be allocated to, (i.e. 10 in each group) it was necessary to keep track of the patients I had seen. This was another challenge as the scores of patients I saw were not known at the time of testing and I needed to find them out afterwards. This needed to be forwarded to me by a medic and was again, very time consuming. It would have been helpful to know the score prior to testing the patients and this is a consideration for further research.

Additionally, with regard to the actual testing sessions, this was fairly long and it felt uncomfortable at times asking patients to complete tasks when they had difficulties. Some grew frustrated and others often wanted to talk about medical complaints or take the opportunity to discuss their personal problems.

Such issues reflect the complexities of performing research in National Health Settings and relying on various team members who are already exceptionally busy and under many demands. As my study did not directly involve such team members, they were still expected to help out and assist and this at time felt difficult to manage. To overcome such difficulties, future studies should perhaps not be carried out unless all staff members are informed of the necessary work involved and are asked about whether they will be able to assist as required. At time sit could feel very daunting when things had not been done and I could feel quite unsupported.

Therefore, various difficulties were encountered with regard to the entire recruitment process. Although this was frustrating at times, I felt the experience helped to develop particular skills such as having to be very well organised, determined and fairly resilient when encountering problems. It was necessary to constantly think in advance and 'chase' things. I found it important to keep up to date with other work that was not beyond my control, such as getting on with written aspects of the thesis. However, I was testing patients more or less up until the deadline of thesis submission and with other demands to meet (new placements, preparing case reports and submission) it was a stressful period.

Nevertheless, I have found the experience worthwhile. I feel that the findings have helped to contribute to some further understanding about liver disease, an important medical condition that affects many people everyday. I feel the research will

be able to help further knowledge and understanding about the impact of early stages of liver disease.

I initially felt that MHE was a rather controversial and vague phenomenon. Although I have a clearer understanding of it, i.e. what possible cognitive deficits are and how they might be caused, I remain feeling that there is further scope for more research. For example, there remains no uniform measure of it or diagnostic tool. The medical complications of MHE remain complex to someone who has studied psychology.

2.0 Expansion of discussion

2.1 Findings

A key finding from the current research was that cognitive deficits in liver disease were not accounted for by emotional factors. It suggests that medical/biological models might provide an explanation of deficits in liver disease as opposed to psychological ones. Deficits on domains of cognitive functioning were observed; patients were significantly worse on tests of executive functioning, psychomotor performance and verbal memory tests compared with controls. Additionally, cognitive functioning was poorer in more severe cases of liver disease. Although a global pattern of cognitive deterioration/functioning was not observed in patients with liver disease, the findings suggest a biological process associated with the disease might explain declines in cognitive functioning.

The finding of cognitive deficits independent of mood supports the work by Forton, Thomas, Murphy, Allsop, Foster, Main, Wesnes and Taylor-Robinson (2003). They found that patients with mild hepatitis C had impairments on concentration and speed of working memory, yet were not significantly or clinically more depressed than

controls. Although the current study differed with regards to type of cognitive impairment observed, it also suggests that deficits were unaccounted for by depression, suggesting a biological/pathological process in liver disease underlies the abnormality or types of deficits observed.

2.2 Mood and cognitive functioning

Much research has demonstrated the impact of mood on cognition. For example, a common finding is the role of attentional biases in trait and state anxiety, with biases in selective attention (Mogg & Bradley, 1999; Williams, Watts & MacLeod, 1997). Stroop studies have shown that people with generalised anxiety have a poorer performance on Stroop tests when required to read out lists of threatening words and this has been interpreted as a bias in selective attention (Mogg & Bradley, 1998). Hyper vigilance has also been widely demonstrated in anxiety (Eysenck, 1992; 1997). The current research does not suggest a role for emotional factors in cognitive functioning in patients with liver disease although this is an issue which would benefit from further research.

2.3 Causes of Deficits

The current study has made a significant contribution to the study of cognitive functioning in liver disease. It has suggested that psychological factors may not be clearly associated with cognitive impairments observed in those with liver disease. The precise causes of cognitive deficits observed in MHE remain unknown. The current study suggests causes stem from biological as opposed to psychological factors. As discussed, they might result from pathogenic processes similar to that occurring in overt HE, but at a milder level. That is, these diseases might directly affect brain function, resulting in cognitive impairment (Collie, 2005). The present study suggests this

impairment might be attributed to frontal lobe damage, which is involved in motor functioning.

Other research has been used to offer an explanation of which brain regions might be affected in liver disease patients to account for cognitive deficits. O'Carroll, Hayes, Ebmeier, Dougall, Muray, Best, Bouchier & Goodwin (1991) found significant overall impairment in cirrhotic patients compared with controls and regional cerebral blood flow was measured. The degree of cognitive impairment was directly correlated with functional abnormalities in the basal ganglia and limbic cortex.

Increased ammonia levels (as outlined earlier) might be one possible explanation. However, other hypotheses have been proposed, such as increased neurotransmitters that are found in various brain regions in excessive quantities, such as increased GABA.

2.4 Future Research and Clinical Implications.

A number of research and clinical implications have arisen from the current research. Further studies can help establish some of the biological causes of liver disease with regards to various toxic substances or pathways involved. They can also help establish types of cognitive deficits in various stages and severity of liver disease. Additionally, future studies could be performed which overcome some of the limitations associated with the current one. For example, one important consideration is that the current study did not account for effects of effort or fatigue. It can be suggested that the patients had a poorer performance on neuropsychological tests as they simply lacked in effort.

Fatigue is also important to consider. Swain (2000) discusses how this is a distressing and very common symptom in chronic disease. However, because of the subjective nature of fatigue, and the lack of effective therapeutics to treat it, the symptom been

ignored by clinicians (Swain, 2000). Recently, fatigue has received greater attention as part of overall health related quality of life assessments in patients with chronic disease. In the current study, fatigue might have played a role when performing tests of motor functioning, for example. Further research could attempt to control for effects of fatigue and effort in order to understand how this may present clinically.

Further research could also look into the type of factors necessary to enable a decent quality of life. As outlined earlier, patients with liver disease have tended to report poorer quality of life status than controls, and the precise reasons for this remain unknown. Studies have tended to illustrate family factors and support networks, yet few have been performed and a wider understanding of some of these factors is required. It is also unknown as to whether disease severity is associated with quality of life as few studies on this have yielded mixed results.

The implications of abdominal pain in liver disease could be further investigated. As outlined earlier, many people with chronic hepatitis experience abdominal pain or discomfort around their liver. Although this has been attributed to many causes (Palmer, 2004) the full consequences of this in terms of cognitive deficits or wellbeing could be investigated further. It can be suggested that if one is in pain, it could impact on both domains either directly or indirectly (i.e. through fatigue or effort).

Indexes of quality of life specific for MHE have not been developed and exactly which aspects of life are affected in the condition is unknown. There are also different therapeutic alternatives for MHE. Improvement in neuropsychological tests has been reported with vegetable protein diets, for example. Those therapies that are active for overt hepatic encephalopathy are also considered valid for MHE. However, another critical question is whether specific therapies should be tailored to suit the individual,

depending on their major individual difficulties. This could involve predominantly low mood, anxieties, cognitive dysfunctions or poor perceived quality of life, etc.

2.5 Strengths and weaknesses

A number of strengths and weaknesses can be identified with the research. Key strengths are that it has provided an understanding of some of the effects liver disease might have on cognitive functioning and the various difficulties people may experience. It has therefore also been a worthwhile and innovative piece of work that can be built upon and developed.

A strength lies in the actual methodology and design. Patients with various stages of liver disease were assessed using a comprehensive neuropsychological test battery and performances on all aspects of neuropsychological functioning were compared. All neuropsychological tests used were well validated and standardised tests that have been widely used in research settings. Additionally, the study incorporated both a between subjects and within subjects design.

A further strength was that additional measures were taken that were concerned with other aspects of psychological functioning and wellbeing. Again, the Hospital Anxiety and Depression Scale is another well respected measure. Therefore, there is plenty of scope to follow up various ideas that has emerged from the research. Few studies, if any have taken such psychological measures so effects of anxiety and depression might have occurred and impacted on test performances.

Although the research can be viewed as a thorough and extensive study, a number of weaknesses can also be identified. The main weakness could be the use of neuropsychological tests to determine functioning or ability. Various confounding factors might have influenced test performance, such as effort and fatigue. Some patients

did not have English as a first language (although were considered fluent in English and appropriate for the study), so various cultural differences might have impacted on their performance. Therefore, future research could consider ways of controlling for this.

A further limitation with the research investigating cognitive functioning in hepatic encephalopathy is that different researchers have used different tests to assess areas of functioning. This makes it difficult to make sensible conclusions about findings and has been acknowledged in the literature.

Another weakness is the small sample with regards to the within subjects (i.e. different patient groups/severity of liver disease) comparisons. In order to make generalisations, more patients could be tested.

Further still, a limitation with the current study was that a measure of overall wellbeing/quality of life was not included and this could be included in future research to gain an understanding of general quality of life. Therefore, future studies should include a measure of this as, although in the current study patients' performances cannot be attributed to either anxiety or depression, other forms of psychological distress might have impacted on their performances yet this was not detected through any particular measure used in the study.

2.6 Summary

In summary, a number of clinical and scientific implications have emerged from this research. Clinically, it is useful to consider deficits patients with liver disease might have and why this might be the case. If patients are experiencing significant cognitive and/or psychological problems, they could be offered various forms of psychological input. For example, if they are having significant memory impairments or

attention/concentration deficits, they could be taught how to use various strategies or techniques to compensate for this.

The research has also contributed to the understanding of the relationship between severity of liver disease and cognitive impairment, with possible explanations of how progression of liver disease might exert effects on functioning.

Further research could also be carried out in order to help determine the extent of cognitive deficits. For example, further studies could use a larger sample size in order to investigate whether observed effects remain. Additionally, effects of fatigue and effort could be controlled for in order to see whether effects remain. Further still, additional measures of quality of life could be used in order to assess whether certain difficulties are commonly reported in various stages of cirrhosis.

Therefore, various inputs from a psychological perspective could be developed in order to answer remaining clinical and scientific issues that have emerged through the current study.

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Appendices

Appendix A: Letter of Ethical Approval

ROYAL FREE AND UNIVERSITY COLLEGE
MEDICAL SCHOOL
DIVISION OF MEDICINE
THE UCL INSTITUTE OF HEPATOLOGY

11TH SEPTEMBER 2006

Dear ,

REC ref N°:
REC name: Committee A
Study Title: A study to assess whether driving hazard perception is impaired in chronic liver disease.

Further to the telephone conversation I had with your colleague, Asha today, below I outline the neuropsychological test battery we will ask our study volunteers to perform. As discussed, this is a minor amendment to incorporate a few standardised tests which will only involve a clinical interview/questionnaire to cover self-reported levels of functioning. The test battery will now take 1 hour rather than the 20 minutes (as previously stated in our earlier ethics submission for just the hazard perception test). Therefore, in addition to the hazard perception test, we wish to now include the following standard neuropsychometric test battery as our neuropsychological outcome measures;

Psychological measures
- Beck Anxiety Inventory
- Beck Depression Inventory

Quality of life
- Sickness Impact Profile

Premorbid Ability and current ability:
- Wechsler test of Adult Reading (WTAR) National Adult Reading Test (NART)/WAIS R

Memory:
Recall and recognition:
- AMIPB (list, story, design, figure, immediate delay, recognition)

Frontal regions:
This will be assessed by the Verbal Fluency (FAS) test and Stroop (subtests from the WAIS)

Motor:
Digit Symbol; Trails A & B, AMIPB (story and figure tests)

If any further information is required please do not hesitate in contacting me to discuss this matter or request further information.

Yours sincerely,

Clinical research fellow (to Dr)

Appendix B: Information Sheet and Consent Form

Appendix 2

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Patient Information Sheet

CIRRHOSIS STUDY

You are being invited to take part in a research study being carried out by a research team from University College London (UCL) and The Institute of Hepatology (IoH). Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

Purpose of the study

The main aim of the study is to assess the impact of cirrhosis on overall wellbeing including general mood and quality of life and their abilities to perform certain tasks.

Background

In patients with cirrhosis of the liver, the toxin ammonia which is normally removed by the liver, builds up. Excess ammonia is associated with a condition called Hepatic Encephalopathy. This is associated with a variety of symptoms and often patients with chronic liver disease suffer from a mild but persistent form of Hepatic Encephalopathy. This can reduce the quality of their lives, impairing concentration and their ability to drive as safely as a patient without chronic liver disease.

The Driving Standards Authority (DSA) requires anyone taking a driving test in the United Kingdom to pass a theory test in additional to the practical component. From 14 November 2002, the theory test has also included a test of hazard perception skills. The hazard perception element consists of 14 video clips, which feature real road scenes and developing hazards of various types, such as vehicles and pedestrians. To pass the hazard perception test, an individual must score 50%.

Therefore, we are also interested in assessing whether patients with liver disease find this test harder and score less well than people who do not suffer from liver disease. This will help us to assess what percentage of patients with liver disease may be affected by Minimal Hepatic Encephalopathy.

Why have I been chosen?

We are interested in assessing the range, nature and extent of possible deficits in patients with different levels of cirrhosis to determine the extent to which it affects everyday lives. Therefore, we have been asking those individuals who are known patients with cirrhosis.

What does the study involve?

You will take part in a clinical assessment and clinical interview. The assessment involves pen-and-paper tests of information processing, including memory and attention. The

interview will ask about your work history, quality of life and psychological wellbeing. You will also be asked to fill in some questionnaires about these aspects of your lives. You will then be asked to undertake a computer based test designed to recreate the hazard perception element of the modern driving test. A low score on this test in no way implies you are a bad or unsafe driver or have failed a driving test. We use the result to give us specific information on attention and perception for research purposes only. You do not need to contact the DVLA as a result of this test and the result **will not** be passed onto any third party or the DVLA.

The appointment will last approximately 1 hour and 30 minutes, (although this might take longer if you require breaks during the session). We will also require information about the severity of cirrhosis, as diagnosed by your consultant.

Expenses

We are able to reimburse any travel expenses incurred by your participation in this study.

Will I be able to see the results of the study and what are the benefits of taking part?

Feedback will be given after the assessment. The results of the study will contribute to the understanding of cirrhosis and help in the development of future treatment strategies and overall support of patients.

What if there is a problem?

Any complaint about the way you have been dealt with in the study or any possible harm you might suffer will be addressed. Please contact the principle investigators, Dr Sarah Mackenzie-Ross ( ) or Dr Oliver Mason ( ).

You must understand that you are under no obligation to participate in this study and if you are unwilling to participate in this study, then it will in no way affect your further management. If during the course of the study you do not want us to continue with the study, we will stop the study at that instant. This study is being performed under the supervision of Dr R Jalan ( ), Dr Sarah Ross ( ) and Dr Oliver Mason ( ). If there are any questions with regard to this study you can speak with him at any stage. Dr S (Consultant Physician, Middlesex Hospital, Mortimer Street,), who is a consultant physician not directly involved with this study, shall be happy to provide independent advice. We can also assure you that all the data acquired from your study will be kept confidential in keeping with The Data Protection Act.

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PATIENT CONSENT FOR CIRRHOSIS STUDY

Name of patient

DOB

Hosp. Number

	(YES/NO)
Have you read the information sheet?	.....
Have you had the opportunity to ask questions?	.....
Have you received satisfactory answers to your questions?	.....
Have you received enough information about the study?	.....
I understand that this is non-therapeutic research from which I cannot expect to derive any benefit	.....

Do you understand that you are free to withdraw from the study:

At any time	.....
Without any reason	.....
Without affecting your future care	.....

Do you agree to take part in the study .....

....

Signature of patient **Signature of investigator**

Date .....

(For information contact Dr)

3 copies to be made:
Top copy to be retained by Investigator
Second copy to be retained by patient
Third copy to be filed in hospital notes