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Hepatitis C, Quality of Life and Cognitive Function : An Exploratory Study

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Hepatitis C, Quality of Life and Cognitive Function: An Exploratory Study

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A report submitted in partial fulfilment of the requirements for the award of Bachelor of Arts (Psychology) Honours, Faculty of Community Studies, Education and Social Sciences, Edith Cowan University.

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Hepatitis C, Quality of Life and Cognitive Function: An Exploratory Study

Active chronic hepatitis C (CHC) is a viral infection that affects approximately 150,000 Australians. It has various quality of life impacts and the literature suggests some cognitive ramifications. In this Western Australian exploratory study, 13 healthy students from Edith Cowan University made up a control group. One experimental group consisted of 11 people with CHC and mild liver damage, and a second experimental group consisted of 8 people with CHC and at least moderate liver damage. The participants were assessed with a health-related quality of life questionnaire, the Short Form 36 Health Survey (SF-36); a test of cognitive functioning, the PSE-Syndrome-Test (PSE-Test); and a test of pre-morbid intelligence, the National Adult Reading Test (NART). One of the aims of the study was to consider the local suitability of these instruments. The control group results on the SF-36 and the NART were as expected compared to relevant norms. The PSE-Test, which has not been used in Australia, performed as expected with one possible difficulty, probably relating to the translation of the instructions from German to Australian. While the tests performed satisfactorily, one of the main conclusions of the study was that cross-sectional survey designs are problematic for research in this area, because of the large number of uncontrollable variables. It is suggested that repeated measures designs are more likely to produce credible results. Due to the exploratory nature of the study, the small number of participants and the lack of control over variables, it was difficult to provide convincing statistics. Nevertheless, the SF-36 results largely followed the pattern established in the literature that points to a diagnosis of HCV as being the most important determinant of health-related quality of life in people infected with the virus. The PSE-Test results, as adjusted by NART covariation, showed no evidence of dysfunction in the cognitive domains of attention, concentration and fine motor control. Indeed, the group with CHC and mild liver damage performed marginally better than the university students. The practical conclusion from this research, and related studies, is that anti-viral treatment should be aimed at the re-establishment of current health-related quality of life, in addition to targeting the preservation of future quality of life.

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Submitted: October 2003

Declaration

I certify that this thesis does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma in any institution of higher education and that, to the best of my knowledge and belief, it does not contain any material previously published or written by another person except where due reference is made in the text.

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Date: 13/1/04

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Hepatitis C, Quality of Life and Cognitive Function: An Exploratory Study

Approximately 3% of the world's population, or 170 million people, are infected by the hepatitis C virus (HCV; Crofts, 2001). Many of these people have hepatitis C-related reductions in quality of life (Bonkovsky & Woolley, 1999; Foster, Goldin, & Thomas, 1998; Miller, Hiller, & Shaw, 2001; Rodger, Jolly, Thompson, Lanigan, & Crofts, 1999). Many also complain of depression, mental clouding and a general inability to function properly (Forton, Taylor-Robinson, & Thomas, 2003) and research has provided some evidence of cognitive changes in hepatitis C–positive people (Forton, Thomas et al., 2002; Hilsabeck, Perry, & Hassanein, 2002; Kramer et al., 2002; Quero, Hartmann, Meulstee, Hop, & Schalm, 1996). Some researchers have noted a relationship between changes in quality of life and changes in cognitive function (Groeneweg et al., 1998). This is not surprising because "Cognitive function refers to those mental processes that are crucial for the conduct of the activities of daily living. Such mental processes include attention, short-term (working) memory, long-term memory, reasoning, the coordination of movement and the planning of tasks" (Wesnes, 2002, p.30).

The current exploratory study considered the practicality of researching the quality of life and cognitive function of HCV-positive people by using a cross-sectional survey design and three instruments, one which has not been used in Australia and one which has not been widely used in Western Australia. This area of research is important because hepatitis C can have a significant impact on well-being and can also result in various insults to the brain. As a consequence, the hepatitis C epidemic provides an excellent opportunity for psychologists to consider certain aspects of brain function and various quality of life issues. There are also

ramifications for the care and treatment of people with HCV. The following introduction will provide a brief overview of hepatitis C and the progression of the infection. The HCV-related literature on quality of life and cognitive functioning will then be reviewed.

A full-scale study published by Córdoba et al. in August 2003, covered similar ground to this present study. In one sense this detracts from the exploratory nature of the current study, however, as there are differences in geography and instruments used, greater breadth has been added to the area of research.

Hepatitis C Epidemiology

Infection with HCV is a leading cause of liver disease, cirrhosis, liver failure, hepatocellular carcinoma (HCC) and it is also the most common reason for liver transplantation in Australia (Farrell & Cossart, 1999). The Hepatitis C Virus Projections Working Group (2002) estimated that approximately 1%, or about 150,000 Australians, have active HCV and that the incidence of new infections in 2001 was 16,000. It is however important to recognise that HCV statistics are particularly problematic, especially the incidence figures, because the infection is often asymptomatic especially in the early stages. Also, HCV is a relatively recently recognised health problem and notifications do not reliably distinguish new infections from the delayed reporting of old infections (Atthowe, Thompson, & Giele, 2003; Staff, Brnabic, Schwarz, & Holt, 2000).

HVC is one of six viral hepatides: A, B, C, D, E, and G (Howard, 2002). Hepatitis A and hepatitis B were isolated in the early 1970s, but it was soon recognised that another viral infection was also causing liver damage. This became known as 'non-A, non-B hepatitis' until it was properly identified in 1989 (Choo et al., 1989). Tests for antibodies to HCV were available in 1989 but these tests, while

cheap, resulted in false positives for the approximately 25% of people who spontaneously clear the virus and false negatives, because it takes four to six months from the time of infection for antibodies to be detectable (Bowden, 2001). In 1990 the polymerase chain reaction (PCR) technique was developed to detect active HCV and according to Bowden the PCR assay is the most commonly used assay for the detection of active HCV in Australia.

Hoofnagle (2002) noted that active HCV has a ribonucleic acid (RNA) genome, which provides the coding for the replication of the virus. This takes place in the cytoplasm of liver cells where the virus does not directly cause liver cell death. In Hoofnagle's view, liver cell damage is caused by rapid virus replication and continuous cell-to-cell spread. The coding sequence of HCV genomes can differ significantly and six major genotypes with more than 50 sub-types have been described. Hoofnagle suggested that the different HCV genotypes are similar in clinical expression with the most important exception being their different responses to interferon treatment.

Crofts (2001) provided an interesting and descriptive history of HCV, going back hundreds of years, and noting wide geographic variations in HCV prevalence, different genotype distributions and different modes of transmission. In Australia, Crofts estimated that genotype 1 accounts for 50 to 60% of all prevalent infection, genotype 2 about 10%, while genotype 3a accounts for 30 to 40%. However, genotype 3a is increasing relative to the other genotypes because it is more recent and is common amongst intravenous drug users. Crofts also pointed out that genotype 4 from North Africa and the Middle East and genotype 6, from South-East Asia, are being more frequently found in Australia due to migration and international travel.

Transmission of HCV is almost entirely, if not always, by blood to blood contact, with percutaneous exposures, such as transfusions with infected blood products, shared drug injection equipment and needle-stick injuries, being the most efficient means of transmitting the virus (MacDonald & Wodak, 1999). The Hepatitis C Virus Projections Working Group (2002) concluded that of those currently living with the virus in Australia, 83% were infected due to unsafe injecting, 5% due to the infected blood supply prior to 1990, and 12% due to other causes such as unsterile body piercing, needle stick injuries, unsterile medical procedures, and transmission from mother to child which may occur in about 2 to 5% of births to mothers with detectable HCV-RNA (Atthowe et al., 2003). It is important to note that HCV is not transmitted through hugging, kissing, cooking utensils, sneezing, coughing, toilets, or drinking glasses and it is only transmitted sexually when there is blood-to-blood contact (Atthowe et al.).

Treatment of Hepatitis C

No consideration of HCV should ignore the great progress that has been made with treatments since the virus was isolated in 1989. There are good prospects of a cure for the majority of infected people and this should condition all thinking about HCV. In the early 1990s limited success was had with the use of interferon (IFN) administered subcutaneously three times per week for 12 months. However, Dore (2001) noted that only about 10 to 20% of patients were HCV-negative as tested by PCR, six months after the end of treatment (a sustained viral response or SVR). By the late 1990s treatment with combination therapy (IFN and ribavirin) resulted in 30% of patients with genotype 1 achieving SVR after 12 months treatment, while patients with genotypes 2 and 3a achieved a 65% success rate after six months treatment (Sievert, 2001). Recent research has concentrated on ribavirin

and IFN with the large polyethylene glycol molecule (Cheng, 2003). Use of this pegylated interferon requires an injection only once per week as it has a slow release that maintains a steady level of IFN in the body. Studies with pegylated interferon and ribavirin suggest that SVR can be expected in approximately 50% of those with genotype 1 after 48 weeks of treatment, and 80% of those with genotype 2 and 3a, after 24 weeks of treatment (Cheng; Fried et al., 2002; Manns et al., 2001). Pegylated interferon is the best treatment available in the United States and many Australians are holding off alternative treatments until pegylated interferon has been approved for use in Australia. Cheng expects approval by late 2003.

Progression of Hepatitis C to Fibrosis/Cirrhosis

Once a person is infected with HCV there is a rapid onset of the acute phase of the infection with HCV-RNA almost always being detectable by PCR within one to two weeks (Hoofnagle, 2002). Liver damage is indicated by an increased release into the blood stream of the enzymes alinane aminotransferase (ALT) and aspartate aminotransferase (AST). Hoofnagle noted that increases in ALT and AST levels in the blood start to rise two to eight weeks after exposure to HCV and symptoms such as malaise, weakness, anorexia and jaundice occur at this stage in approximately one third of infections. The symptoms, if any, last for three to four weeks after which they decline along with ALT and AST levels. In about 25% of cases HCV infection resolves itself (Alter et al., 1999) and Hoofnagle pointed to some evidence suggesting that spontaneous resolution occurs more frequently in young people, women, and ironically, in people whose acute symptoms are more severe. If resolution of the infection is not achieved within six months then the infection is taken to be chronic and the spontaneous resolution of chronic hepatitis C (CHC) is unusual (Yokosuka et al., 1999).

Once chronic infection has set in, the major issue is fibrosis and its potential progression to cirrhosis and end-stage liver disease, or hepatocellular carcinoma (HCC). Fibrosis is the result of a sustained wounding/healing process that initially causes inflammation of the liver. If the process continues, scarring may bring about changes to liver architecture and the deterioration of liver functions that include blood detoxification, glucose storage, the synthesis of bile precursors, and the manufacture of blood coagulation factors and neurotransmitter precursors (Tarter, Edwards, & Van Thiel, 1988).

For people with HCV it is important to assess the degree of liver damage. Some idea can be gained by ALT and AST levels in the blood, but these serum markers fail to discriminate accurately between different fibrosis stages. At present the only reliable way to assess liver damage is by sampling the liver with a biopsy (Friedman, 2003). Histological examination results in the staging of the fibrosis, by using the Metavir score (four stages), or the modified Knodell system (Ishak et al., 1995). The seven stages of the Knodell system ranging from 0 (no fibrosis) through varying degrees of structural liver damage to stage 6 (cirrhosis) are detailed in Appendix A. In this thesis 'mild chronic HCV' will include Knodell stages 0 to 2. The term covers inflammation of the liver tracts, but no partial blocking or bridging of the tracts. 'Moderate chronic HCV' will include Knodell stages 3 to 5 which is to the point when there is marked bridging or partial blocking of the tracts. Knodell stage 6 fibrosis (cirrhosis) includes the formation of nodules that block the liver tracts and impedes blood flow in the liver.

It is impossible to generalise about the rate of progression of fibrosis and many studies have been done on different populations and by using different research designs. In an effort to bring meaning to this area of research Freeman et al. (2001)

analysed 57 studies which were divided into: a) cross-sectional studies of people referred to liver clinics; b) longitudinal studies of people with post-transfusion HCV; c) cross-sectional surveys of persons newly diagnosed at blood donor centres; and d) longitudinal community-based research such as studies of people followed up after proven acute infection. Freeman et al. (2001) found in their review, that estimates of progression to cirrhosis after 20 years from infection was 22% in the liver clinic studies, 24% in the post-transfusion studies, 4% for the blood donors and 7% in the community-based studies. These findings are consistent with both Poynard et al. (2001), who estimated that on average 9% of those with CHC become cirrhotic in 20 years from infection and 44% in 40 years, and also Alberti and Benvegnù (2003) who concluded that about 20% of those with CHC progress to cirrhosis (Knodell stage 6). Freeman et al. (2001) also confirmed the research of Poynard et al. (2001) in finding that three factors were associated with faster fibrosis progression; older age at time of infection, alcohol consumption of 50g or more per day and male gender.

One of the concerns of some HCV research is the single categorisation of cirrhotics. In clinical practice in Australia it is common to distinguish between three groups of cirrhotics by using the Child-Pugh classification (W. D. Reed, personal communication, May, 2003). The classification relies on assessing: a) overt cognitive impairment which is almost certainly caused, in part, by the inability of the liver to clear toxins from the blood; b) abnormal fluid levels in the peritoneal cavity (ascites) due mainly to the obstruction of portal vein blood flow through the damaged liver; c) excessive bile in the blood (jaundice) which is caused by the inability of the damaged liver to process the bile appropriately; d) inadequate manufacture, by the liver, of albumin causing oedema; and e) increased bleeding-

time due to the liver's failure to manufacture clotting agents (Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973).

When the patient is cirrhotic (Knodell stage 6), but the assessment of functions by the Child-Pugh classification is favourable, then the patient is considered to have compensated cirrhosis and is classified as Child-Pugh A. However, when the assessment is unfavourable the patient is considered to have decompensated cirrhosis and the classification will almost certainly be Child-Pugh B/C. In patients with decompensated cirrhosis, episodes of ascites, jaundice, cognitive impairment or gastrointestinal bleeding can be expected to start and Fattovich et al. (1997) found that after the first decompensation episode the probability of survival for 5 years was 50%.

Friedman (2003) estimated that 40% of Child-Pugh A cirrhotics are asymptomatic and therefore they are probably outside the health system. Studies with consecutive cirrhotic patients attending outpatient clinics indicate that about 75% of patients under health care are Child-Pugh A (Groeneweg et al., 1998; Quero, et al., 1996; Romero-Gómez, Boza, García-Valdecasas, García, & Aguilar-Reina., 2001). Thus, about 25% of the 60% of cirrhotics receiving medical attention, or 15% of all cirrhotics, are Child-Pugh B/C. The Hepatitis C Virus Projections Working Party (2002) has published similar, but not identical figures (Table 1; p.15).

In summary, the progression of hepatitis C can be divided into the following broad phases; the acute phase, and if the infection does not spontaneously resolve itself the infected person will move to the CHC phase, firstly with mild chronic HCV (Knodell stages 0 to 2), possibly progressing to moderate chronic HCV (Knodell stages 3 to 5) and then possibly to Child-Pugh A cirrhosis and finally to Child-Pugh B/C cirrhosis. Putting numbers to this progression can only be done as a gross

generalisation, but such generalisations give some idea of magnitude. Of say, 100 people who become infected with HCV, 25 of them will spontaneously clear the virus and 75 will progress to CHC. Of this 75, about 15 will progress to Child-Pugh A cirrhosis over a variable, but extended period of time, perhaps as long as 40 years. Of the approximately 15 people who progress to Child-Pugh A cirrhosis, and again over an extended period of time, perhaps two people will progress to Child-Pugh B/C cirrhosis. In the meantime, less than one person will develop hepatocellular carcinoma (HCC).

HCV and Health-Related Quality of Life (HRQOL)

Quality of life is concerned with general wellbeing, health, activity level, social support, personal resources, accomplishments and spirituality (Koff, 1999). However, in health care settings Koff noted that a more narrowly defined health-related quality of life (HRQOL) has been increasingly used in medical decision-making and research. With the patient being the focal point, a good HRQOL means good physical and emotional functionality and wellbeing. As Koff and Owens (1998) have pointed out, HRQOL encapsulates, and in a sense summarises, all the physical and mental symptoms being experienced by an individual. Thus, measurements of HRQOL can be used to consider and compare different health conditions and the outcomes of medical interventions. Forton, Thomas, Taylor-Robinson (2003) noted that the usual quantitative measure of health status for HCV research is the Short Form 36 Health Survey (SF-36; Ware, Snow, & Kosinski, 2000). This instrument provides scales for eight health dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health, and summary scores for physical and mental components.

It is almost impossible to consider HRQOL in the approximately 58,000 Australians with CHC who have not been diagnosed (Hepatitis C Virus Projections Working Group, 2002). There is some limited evidence that these people may have small decrements in HRQOL (Dunne & Quayle, 2001; Rodger et al., 1999). However, it is not until HCV has been diagnosed that participants can be recruited for larger scale studies. Such studies have convincingly shown that an HCV-positive diagnosis is a significant determinant of reduced HRQOL.

Possibly the best of these studies (Koff, 1999), was by Bonkovsky and Woolley (1999). They recruited 358 Child-Pugh A cirrhotics and 284 non-cirrhotic people from the United States and Canada. HRQOL instruments included the SF-36. The questionnaires were self administered by the participants at baseline and after 24 weeks of interferon monotherapy, but before participants found out whether or not they had cleared the virus. The baseline results were compared with 750 healthy controls who had significantly higher (better) scores ($p < .001$) on all eight scales of the SF-36. This cross-sectional analysis with such numbers is important research, but Bonkovsky and Woolley also used an even more convincing repeated measures analysis for one aspect of the study. They waited six months after treatment to determine which patients had a sustained HCV-negative response (SVR). The results for these SVRs were analysed and there were statistically significant SF-36 differences from the healthy controls at baseline. However, these differences were reduced to below the level of significance by the end of treatment, except on one scale, general health. The decrement of HRQOL at baseline, plus the marked improvement after successful treatment, for the SVRs, provided convincing support for the hypothesis that those people diagnosed with hepatitis C have a significant deterioration in HRQOL and that this improves with the eradication of the virus.

The Bonkovsky and Woolley (1999) research leaves the remote, but logical possibility, that the HCV-positive participants had significantly reduced HRQOL prior to diagnosis. However, the Australian study by Rodger et al. (1999) specifically underscores the potency of an unfavourable diagnosis. The researchers used stored frozen serum from 238 patients who were diagnosed with acute viral hepatitis between 1971 and 1975 at the Fairfield Infectious Diseases Clinic in Melbourne. By 1999 some of these people had been located and assessed by a variety of instruments including the SF-36. Candidates were excluded if they were not HCV-positive, had cirrhosis, had any overt clinical symptom of liver disease, or had medical conditions other than HCV. After the exclusions, 34 participants remained; 19 were not aware that they were HCV-positive prior to SF-36 testing, and 15 knew of their HCV status. The participants who were aware of their HCV-positive status before testing, scored significantly worse, on all eight scales of the SF-36 than the participants who were unaware of their HCV-positive status, even after adjustments were made for age, sex, marital status and ALTs. This study of two well-matched groups convincingly showed that people who are aware of an HCV-positive diagnosis perceive their functionality and well-being to be less than people who have been HCV-positive for the same period of time, but who are not aware of their HCV status.

It is in fact unremarkable that a diagnosis of HCV results in an immediate reduction in HRQOL. Qualitative research has clearly shown that such a diagnosis brings with it feelings of uncertainty, fear of death, transmission concerns, depression, worry about cognitive changes, discrimination concerns, a reduction in roles because of fatigue and also relationship problems (Dunne & Quayle, 2001; Glacken, Kernohan, & Coates, 2001; Hepworth & Krug, 1999). Such qualitative

work is supported by a number of quantitative studies. Fatigue and emotional stress, particularly depression, are the major symptoms reported in such studies. Lee, Jamal, Regenstein, and Perrillo (1997) found that 45% of their 500 CHC participants related a history of chronic fatigue and 24% of the untreated participants had depression. Fontana et al. (2002) concluded that 35% of their CHC participants had clinically significant emotional distress compared to an expected frequency of 10%, while Gifford, O'Brien, Bammer, Banwell, and Stoove (2003) in Australia, reported that 58% of 462 women reported symptoms relating to HCV, mainly tiredness and nausea. Another Australian study, McDonald, Jayasuriya, Bindley, Gonsalvez, and Gluseska (2002) found that approximately 50% of the 76 men and 39 women had significant levels of depression, anxiety, somatization, interpersonal sensitivity and hostility. The authors concluded that there was a strong correlation between fatigue and psychopathology, but not between fatigue and disease activity. However, they stopped short of concluding that fatigue was caused by psychopathology rather than disease severity. Wessely and Pariante (2002) on the other hand, reviewed the literature and concluded that there was no evidence of an association between HCV-infection per se and fatigue or depression.

After the HRQOL decrements associated with a positive HCV diagnosis, the literature suggests that HRQOL does not change much even when the HCV progression extends to early cirrhosis. In the previously cited study by Bonkovsky and Woolley (1999) the 358 Child-Pugh A cirrhotics and the 284 non-cirrhotic participants were compared at baseline and the non-cirrhotic patients had SF-36 scores that were only slightly better and of a similar pattern to the cirrhotics. Similar findings have been reported by Miller et al. (2001). They administered the SF-36 to 95 untreated CHC patients attending two South Australian day clinics. It was found

that SF-36 scores did not differ significantly according to ALT levels. Foster et al. (1998) also obtained similar results in a comparison of a mild liver disease group (Knodell stage 2 and less) and those with moderate liver disease (Knodell stage 3 to 5). Results on five of the SF-36 scales were in the direction of a lesser HRQOL for the moderate liver damage group, but the differences did not approach statistical significance.

Once Child-Pugh A cirrhosis is reached there is some evidence to suggest that a small proportion of people suffer HRQOL decrements because of deteriorating cognitive function. In a study by Groeneweg et al. (1998) 136 Child-Pugh A cirrhotics and 43 Child-Pugh B/C cirrhotics completed the Sickness Impact Profile (SIP; Bergner, Bobbitt, Cartner, & Gilson, 1981). This 136 item HRQOL questionnaire assesses 12 areas of daily functioning; social interaction, alertness behaviour, emotional behaviour, communication, ambulation, mobility, body care, sleep and rest, work, home management, recreation and pastimes, and eating. The participants in the Groeneweg et al. research were also given the Number Connection Test Part A (Conn, 1977), the Digit Symbol Test (Wechsler, 1955) and an electroencephalogram (EEG). If one or more of these tests were abnormal then cognitive impairment was diagnosed. Of the 136 Child-Pugh A cirrhotics, 25 (18%) were diagnosed with cognitive impairment and of the 43 Child-Pugh B/C cirrhotics, 23 (53%) were cognitively impaired. The 48 who were diagnosed with impairment reported significant reductions on all 12 scales of the SIP compared with the group without impairment.

In summary, there is possibly a small reduction in HRQOL for those with undiagnosed HCV and if there is, then presumably this is due to an as yet unidentified biological mechanism. A larger decrement occurs after diagnosis when

psychosocial factors become relevant. There is little change in HRQOL between people with mild chronic HCV and those with moderate chronic HCV. There is possibly some further decrement in people with Child-Pugh A cirrhosis, although this decrement may only be experienced by the few Child-Pugh A cirrhotics who experience cognitive dysfunction. Once the liver disease progresses to Child-Pugh B/C there is a very considerable reduction in HRQOL because such people will have, or will shortly have, the serious consequences of decompensation, such as overt cognitive dysfunction, jaundice, gastrointestinal bleeding and ascites.

This pattern of HRQOL decrements has been quantified in Australia by the Hepatitis C Virus Projections Working Group (2002). They estimated HRQOL adjustments in order to calculate quality of life years lost due to HCV infection. The HRQOL adjustments in Table 1 are taken from Table 9 of the Working Group's Report, (p. 25). The HRQOL adjustments were largely derived from a panel of hepatologists (Bennett et al., 1997). The adjustments are somewhat smaller than suggested by patients in a study comparing judgements by hepatologists and patients (Cotler et al., 2001). Nevertheless, they reflect a consensus pattern that has been recently reaffirmed by Córdoba et al. (2003). These researchers recruited four groups of 40 participants. Each group had a different HCV status: good health, mild HCV, Child-Pugh A cirrhosis, or Child-Pugh B/C cirrhosis. The only difference between Córdoba et al. (2003) and the estimates of the Hepatitis C Virus Projections Working Group (2002), was that the latter authors showed a significant reduction of HRQOL for Child-Pugh A cirrhotics compared to those with moderate HCV. Córdoba et al. (2003) did not find this decrement.

Table 1

Estimated HRQOL Adjustments due to HCV Infection - Australia

HCV infection progression	Knodell Fibrosis Stage	Estimated Persons 2001	HRQOL Adjustments[a]
Mild Chronic HCV - Undiagnosed	0 - 2	50,000	6%
Mild Chronic HCV - Diagnosed	0 - 2	74,000	18%
Moderate Chronic HCV - Undiagnosed	3 - 5	7,000	6%
Moderate Chronic HCV – Diagnosed	3 – 5	20,000	18%
Compensated Cirrhosis – Undiagnosed	6 (A)[b]	1,000	16%
Compensated Cirrhosis – Diagnosed	6 (A)[b]	4,100	26%
Decompensated Cirrhosis – Diagnosed	6 (B/C)[b]	1,300	68%

Note.
[a]The adjustment, or discount, required to enable comparisons of quality of life years between HCV-positive and healthy persons. [b]Child-Pugh classification in brackets.

HCV–Related Liver Disease and Cognitive Function

It has been well established that clinically overt cognitive dysfunction is sometimes found in people with a non-functional (decompensated) liver and one of the main causes of decompensation is CHC (Mullen & Dasarathy, 1999). This clinically observable dysfunction will be called overt hepatic encephalopathy (oHE). Detailed in Appendix B are the different types of oHE and the nomenclature recommended in the Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna 1998 (Ferenci et al., 2002). This Working Party stated that oHE is a neuropsychiatric disorder that involves "...cognitive, affective/emotional, behavioural, and bio-regulatory domains. Different traits can be defined within each domain. For example, cognition may include evaluation of psychomotor speed, visuopraxis, attention, concentration, abstracting, and a level of consciousness" (p. 718).

The oHE syndrome is normally graded in severity from 1 to 4 by the West Haven Criteria (Appendix C; Ferenci et al., 2002). These authors also noted that the most common type of oHE: episodic hepatic encephalopathy, is coded as 'Delirium Due to a General Medical Condition (Code 293.0)' in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV; American Psychiatric Association, 1994). Other DSM-IV codings are discussed in detail by Wiltfang, Nolte, Weissenborn, Kornhuber, and Ruther (1998).

The pathogenesis of hepatic encephalopathy has not yet been fully determined, but what is definitely implicated, is the action of gut-derived ammonia and other neuro-toxins that have not been metabolised by the badly damaged liver (Butterworth, 2002; Häussinger, Schliess, & Kircheis, 2002). The neuro-toxins pass through the blood brain barrier and almost certainly cause swelling in Alzheimer

type 11 astrocytes, particularly in the basal ganglia (Weissenborn & Kolbe, 1998). Weissenborn and Kolbe suggested that the swelling of these astrocytes causes disturbances in neurotransmission that in turn results in changes to sleep patterns, behavioural disinhibition, psychomotor slowing, loss of intellectual flexibility, loss of concentration, and neuro-muscular symptoms including the inability to co-ordinate muscle activity (ataxia), clumsy hand syndrome (dysarthria), and involuntary motor movements especially in the hands (asterixis). These symptoms are similar to many of those exhibited in other subcortical dementias such as Parkinson's dementia and Huntington's chorea (Brown & Marsden, 1998; Middleton & Strick, 2000; Turner, Moran, & Kopelman, 2002). An interesting review of 17 patients with oHE was provided by Summerskill, Davidson, Sherlock, and Steiner (1956) and a précis is in Appendix D.

The oHE syndrome has been considered in some detail largely because it provides a picture of where the syndrome's precursor, minimal hepatic encephalopathy (mHE) is heading (Romero-Gomez et al., 2001). This early phase of hepatic encephalopathy was first recognised by Zeegen, Drinkwater, and Dawson (1970) who found cognitive impairment in cirrhotic patients who did not have oHE (Conn, 1994). The disorder was then usually called 'sub-clinical hepatic encephalopathy' but Ferenci et al. (2002) recommended the term 'minimal hepatic encephalopathy' largely to remove the implication that the disorder had no clinical significance. After a number of studies confirming the existence of mHE a definition was given by Gitlin (1988). This is still used today (Das, Dhiman, Saraswat, Verma, & Naik, 2001). Gitlin's definition was "a condition in which patients with cirrhosis, regardless of its etiology, demonstrate a number of quantifiable neuropsychological

defects, yet they have a normal mental and neurological status to clinical examination"(p. 8).

There has been much variation in the reported prevalence of mHE in cirrhotics. Also, many authors appear to extrapolate to all cirrhotics, the results obtained from studies of Child-Pugh B/C cirrhotics. Consequently, mHE prevalence figures of up to 80% of all cirrhotics have been implied (Kircheis, Wettstein, Timmermann, Schnitzler, & Häussinger, 2002). Few researchers have clearly studied mHE in different Child-Pugh classifications, but Quero et al. (1996) estimated that 14% of Child-Pugh A cirrhotics and 45% of Child-Pugh B/C cirrhotics had mHE. However, Das et al. (2001) concluded that the prevalence of mHE was 56% in Child-Pugh A, 65% in Child-Pugh B, and 64% in Child-Pugh C. As is the case with nearly all work on mHE, it is almost impossible to comment on such varying estimates as different methodologies, different patient groups and different tests for assessing mHE have been used (Weissenborn, 2002). However, the issue is important because the Hepatitis C Virus Projections Working Group (2002) estimated, for 2001, that 6,400 Australians had cirrhosis, but of these only 1300 had Child-Pugh B/C cirrhosis. Using the prevalence figures from Quero et al. about 700 Australians with Child-Pugh A cirrhosis might have mHE. In contrast the Das et al. figures would suggest that there would be about 2,800 with mHE.

While there may be differing conclusions about the prevalence and distribution of mHE, there is consensus that mHE definitely does exist, but this consensus only relates to cirrhotic people. However, a recent study by Hilsabeck et al. (2002) suggested that pre-cirrhotic HCV-positive people might have mHE. This study was concerned with some of the questions being considered by the current research. A quotation from the introduction is of interest:

> In patients with cirrhosis and end-stage liver disease, neuropsychological impairment has been well documented. ...in patients with HCV infection, it often takes more than 20 years of chronic hepatic injury before the liver develops cirrhosis and its complications. During this time, liver function is impaired, albeit slightly. The possibility that cognitive dysfunction may result from slight impairment of liver function, even before the development of cirrhosis, has not been well examined, ... (p. 440).

Hilsabeck et al. (2002) took a random sample of 269 people from patients attending an outpatient clinic at the University of California. After significant attrition and exclusions, the researchers were left with three groups; hepatitis C only (n = 44), hepatitis C plus another chronic illness (n = 22) and a group with non-HCV-related liver disease (n = 14). These participants were also split between non-cirrhotic (n = 40) and cirrhotic people (n = 34). The authors concluded, among other things, that a significant percentage of non-cirrhotic patients had cognitive deficits in the domains of attention, concentration, visual scanning, psychomotor speed and mental flexibility, as measured by the Digit Cancellation Test (Franklin, Heaton, Nelson, Filley, & Seibert, 1988), the Trail Making Tests A & B (Reitan & Wolfson, 1993), and the Symbol Digit Modalities Test (Smith, 1982). No deficits were found in the non-cirrhotic patients in the domains of memory and visuoconstructional abilities as measured by a modified version of the Rey Complex Figure Test (Franklin et al.). In addition the researchers found no significant cognitive differences between the 'hepatitis C only group' and the 'non-HCV liver damage group' which emphasised liver damage per se as the determinant of cognitive

dysfunction and detracted from a recent suggestion that the HCV virus directly attacks the central nervous system.

The Hepatitis C Virus and the Central Nervous System (CNS)

To recap, there can be no doubt that a liver seriously compromised by HCV-related damage can cause encephalopathy. The issue of importance regarding encephalopathy is how much liver damage is necessary to cause mHE? Up until the research by Hilsabeck et al. (2002) there was consensus that liver damage had to be at least to the stage of Child-Pugh A cirrhosis. The article by Hilsabeck et al. has raised a concern that mHE may extend backwards in the progression of HCV to people with moderate chronic HCV.

Recently however, an even more pervasive threat has been raised. It has been suggested by Forton, Thomas et al. (2002) that people with HCV may be exposed to an encephalopathy caused by a direct viral attack on the nervous system (HCV encephalopathy-HCVE). In their research 27 HCV-positive people and 16 HCV-cleared people were given, among other tests, the National Adult Reading Test (NART; Nelson & Willison, 1991), the Number Connection Tests A & B (NCT A & B; Conn, 1977) and the Digit Symbol Test (Wechsler, 1955). Both groups had a high proportion of professional and skilled participants and the mean NART IQ equivalent scores were 117 for the HVC-positive group and 115 for the HVC-cleared group. The authors did not detail the results for the paper and pencil tests but noted, "there were no statistically significant differences between the study groups on any of the paper-based tasks" (p. 435). Wesnes (2002) suggested that the reason for there being no deficits was because the paper and pencil tests were not sufficiently sensitive.

For this reason the two groups in the Forton, Thomas et al. (2002) study also completed the Cognitive Drug Research Computerised Assessment Battery (CDR-Battery; Kennedy, Scholey, Tildesley, Perry, & Wesnes, 2002). This battery has been used in the psychopharmacology field in repeated measures studies to test the cognitive effects of drugs and herbs (Kennedy, Scholey, & Wesnes, 2002; Kennedy Scholey, Tildesley et al., 2002; McKeith et al, 2000; Siegfried, 1993). The battery uses desktop computer presentations to assess four domains: speed of attention (reaction times and digit vigilance), accuracy of attention (accuracy on digit vigilance and choice reaction times), quality of memory (word, picture, number, and spatial memory-immediate and delayed recall), and speed of memory (time taken on memory tasks). The HCV-positive group in the study scored significantly worse than the HCV-cleared group on two factors, speed of attention and speed of memory processes, and in a subsequent review Forton, Taylor-Robinson, and Thomas (2003) further described these deficits as being "selective impairments of attention, concentration and psychomotor speed" (p. 83).

Forton, Thomas et al. (2002) also took a subset of 17 of the HCV-positive participants and found that they had proton magnetic resonance spectroscopy results showing metabolite abnormalities in the basal ganglia. These neurophysiological findings were supported by Kramer et al. (2002). They studied 100 HCV-positive people by using P300 event-related brain potentials (Weissenborn et al., 1990). Seventeen of the participants had prolonged P300 latencies that reportedly correlate with information processing speed, and reaction time. The authors concluded that people with HCV could have a slight but significant neurocognitive impairment that was not related to stage of infection, severity of fatigue, or mental health impairment.

A third group of authors (Krause et al., 2001) has also suggested CNS involvement in HCV infection. These authors studied 30 HCV-positive people with normal ALTs and ASTs and found that half the participants suffered from chronic fatigue as measured by the Fatigue Impact Scale (FIS; Fisk et al., 1994). They then found that these fatigued HCV-positive participants performed poorly on attention and memory tests, not specified in the short poster session report. The conclusion that HCV causes CNS involvement, which then causes fatigue, is clearly at odds with the previously cited review by Wessely and Pariante (2002).

HCVE, if it exists, is clearly a syndrome awaiting definition, just as minimal hepatic encephalopathy was 33 years ago. Much work has to be done to define the characteristics of HCVE because at present only one behavioural test and two physiological tests have been used to define the disorder. The behavioural test; the CDR Battery appears not to be well known or included in reference works such as Lezak (1995) or Spreen and Strauss (1998). The neurophysiological tests, as far as is known, do not have well documented behavioural correlates. By contrast, mHE has been much studied and its neuropsychological characterisation is available for examination.

Neuropsychological Characterisation of mHE

The first attempt to characterise mHE utilised the Trail Making Tests (TMT). These were used by Zeegen et al. (1970) who concluded that a combined time of 130 seconds on TMT A and B distinguished between cirrhotics with and without mHE, given the exclusion by clinical examination of cirrhotics with oHE. Conn (1977) reported that he used the TMT tests, but found that practise effects distorted results when the tests were administered serially to the same person. Consequently, Conn modified the TMT and constructed four different, but equivalent versions and called

them the Number Connection Tests (NCT). By the early 1990s Conn (1994) noted that either the TMT or NCT had been used in nearly all studies of mHE since 1970.

In reviewing the mHE literature Conn (1994) not only found that the TMT and NCT were widely used, he also found that a large number of other instruments were used. He made the point that the sheer diversity of data made it impossible to analyse and compare studies. An increasing realisation of this problem led to the presentation of three papers at the Ninth International Symposium on Ammonia in 1996. These papers aimed at clarifying the neuropsychological dimensions of mHE and they all presented studies in which participants with cirrhosis completed comprehensive test programmes. From these test programmes shorter batteries were developed with a high sensitivity and specificity to mHE (Còrdoba, McCrea, Vessey, Blei, & Randolph, 1997; Watanabe et al., 1997; Weissenborn et al., 1997). By 1999 the work presented by Weissenborn et al. (1997) culminated in the publication in Germany of the PSE-Syndrome-Test (PSE-Test; Schomerus, Weissenborn, Hamster, Rückert, & Hecker, 1999). This test was subsequently recommended for use in mHE research by a consensus group of international experts formed at the 11th World Congresses of Gastroenterology, 1998 (Ferenci et al., 2002).

Describing the PSE-Test Weissenborn, Ennen, Schomerus. Rückert, and Hecker et al. (2001) wrote that it "examines motor speed and accuracy, visual perception, visuo-spatial orientation, visual construction, concentration, attention and to a lesser extent, memory. None of the tests is a true classical test of attention. However, a successful performance of all tests requires an unimpaired attention ability" (p. 771). This characterisation of mHE followed closely Lezak's 1995 description of the cognitive aspects of subcortical dementia "... cognitive dysfunction typically appearing as slowed mental processing, disturbances of attention and

concentration, executive disabilities including impaired ability to manipulate concepts or to generate strategies, visuospatial abnormalities, and a memory disorder that primarily affects retrieval rather than learning" (p. 221). The correspondence of these two passages is not surprising because of the implication of the basal ganglia in the pathogeneses of mHE as previously discussed.

The PSE-Test clearly does not attempt to directly assess the complex and subtle emotional changes of subcortical dementias which are seen mainly as apathy and depression (Lezak, 1995). Nevertheless, these mood-states do contribute to test performance through the mediation of motivation and attention. The question of whether the PSE-Test is a good test of attention and concentration was the subject of a paper by Weissenborn, Heidenreich, Ennen, Rückert, and Hecker (2001). In this study people with poor PSE-Test results also did badly on a wide range of well-recognised attention tests. In a recent article Weissenborn, Heidenreich, Giewekemeyer, Rückert, and Hecker (2003) addressed the relationship between the PSE-Test and the traditional memory tests. Weissenborn et al. concluded that people with mHE do perform poorly on some memory tasks, but largely because of deficits in attention and visual perception. The emphasis on motor deficits in the PSE-Test is consistent with Lezak's conclusion that such deficits are the first indicators of subcortical disorders.

There are five paper and pencil sub-tests in the PSE-Test and the best known is the Digit Symbol Test (DST; Wechsler, 1981). The PSE version of the DST is almost identical to the WAIS-R sub-test. In the DST symbols are related to numbers and the coding rules are established at the top of the page. The participant is asked to code the correct symbols into rows of numbered boxes. The test score is the number of symbols coded correctly in 90 seconds. Lezak (1995) noted that the DST is the

most sensitive to brain damage of any of the Wechsler tests, that it is extremely sensitive to dementia, being one of the final WAIS-R tests to decline, and it is also one of the few Wechsler tests on which Huntington patients perform poorly before overt manifestations of the disease. Wechsler noted that the Digit Symbol Test's correlation with the WAIS-R full-scale score is $r = .57$.

NCT A and NCT B are also included in the PSE-Test. These TMT type tests are simple tests that take between five and ten minutes to administer (Spreen & Strauss, 1998). The TMT-A and NCT-A ('A' tests) require the participant to draw a line as quickly as possible to consecutively join the numbers 1 to 25. The test result is the time needed to perform the task. The skills required are visuospatial scanning, motor speed, alertness, some planning ability, and good motivation (Lezak, 1995; Spreen & Strauss, 1998). The TMT-B and NCT-B ('B' tests) require the participant, as quickly as possible, to connect numbers (1 to 13) and letters (A to L) in an alternating sequence (1, A, 2, B,... L, 13.). The 'B' tests require the same skills as the 'A' tests, but there are additional higher skills needed because it is necessary to hold two sets of information and switch between them (Corrigan & Hinkedley, 1987).

As well as being used to assess brain damage (Reitan, 1958) the TMT type tests have been used to assess chemical insults and drug abuse (Hartman, 1995), mild head trauma (Mathias & Coats, 1999), and certain types of medically induced brain injury (Farmer, 1994). The TMT tests are widely used in Australia and only four other instruments are used more frequently by neuropsychologists (Sullivan & Bowden, 1997).

When the PSE-Test was being developed in the mid-1990s the test programme that was used by Schomerus and Hamster (1998) tested similar skills to the programmes used by Córdoba et al. (1997) and Watanabe et al. (1997), but they also

drew on Edwin A. Fleishman's work in isolating separate psychomotor skills (Fleishman, 1954; Fleishman & Ellison, 1962). Schomerus and Hamster found two psychomotor factors in particular that helped to discriminate between healthy controls and people with mHE. These were, firstly the motor speed and coordination as required by the ability to 'dot' or 'tap' with rapid repetitive movements of the fingers and wrist, and secondly the motor speed and steadiness of arm and hand required for peg board tasks and drawing accurately between two lines. Schomerus and Hamster then modified some of the Fleishman tasks to test for these factors. The two paper and pencil tests were called Serial Dotting and Line Tracing. The Serial Dotting Test asks the participant to place a dot inside each of 100 circles as quickly as possible. The Line Tracing Test requires the participant to draw a continuous line between two parallel lines in a maze-like pattern. The participant needs to go as fast as possible without touching or crossing the parallel lines. These two psychomotor tests were included in the PSE-Test along with the NCT A, NCT B and the DST.

The PSE-Test has been derived from 30 years of work to characterise mHE. It has been recommended for use in studies of mHE by most of the leaders in the field of hepatic encephalopathy (Ferenci et al., 2002) and it should be used with a high degree of confidence. It also includes sub-tests that are widely used to assess generalised brain function.

Research Questions

This was an exploratory study and it was important to consider whether the instruments used performed satisfactorily in the Western Australian environment and whether the study design was satisfactory.

Regarding substantive HCV issues, this research was aimed at enhancing knowledge about the following hypotheses: a) HRQOL decreases when a diagnosis

of HCV infection is received; b) subsequent to the decrement associated with diagnosis, HRQOL remains constant until liver damage causes overt failures of liver functioning; c) in people with mild HCV (Knodell stages 0 to 2), changes to the central nervous system result in cognitive dysfunction; d) mHE is found in HCV-positive people with moderate fibrosis (Knodell stages 3 to 5) and Child-Pugh A cirrhosis; and e) reduced HRQOL is associated with cognitive dysfunction.

Method

Study Design

The current study used a one-way, between-subject design. The independent variable, HCV status, had three levels: no HCV or other health problems; mild chronic HCV (Knodell fibrosis stages 0 to 2); and moderate chronic HCV (Knodell fibrosis stage 3 to Child-Pugh A cirrhosis). The dependent variables were scores on the SF-36 and the PSE-Test. The NART was administered as a potential covariate.

Participants

To form the healthy control group, contact was made with student volunteers on the Edith Cowan University School of Psychology Participant Research Register. To match as closely as possible, the expected demographics of the patient groups, the ten females on the Participant Research Register over the age of 40, and the 12 males on the Register over the age of 25, were targeted. From those who could be contacted, and reported no physical or mental health problems, 15 students agreed to participate and were tested. Two were excluded because of health problems that became apparent at the testing sessions. The final healthy control (n = 13) consisted of five females (mean age = 46.40; range 43 to 50) and eight males (mean age = 32.00; range 24 to 42).

The two HCV-positive groups were recruited from the patients of a medical consultant at the Hollywood Private Hospital Specialist Centre. Patients were not considered for recruitment if there was any clinically observable cognitive dysfunction (oHE), or any comorbidities that seemed likely to affect cognitive function. Patients were also excluded if they had English language difficulties, although two patients were recruited whose English was competent, but whose main education was in a non-English speaking country. Knodell fibrosis stage was

determined largely by liver biopsy although some biopsies were performed some years ago.

After exclusions, a random sample of patients with mild HCV were contacted and 11 agreed to participate. This mild HCV group consisted of six females (mean age = 44.00; range 40 to 49) and five males (mean age = 46.40; range 35 to 56). After exclusions, all patients with moderate HCV were contacted and eight agreed to participate. The moderate HCV group consisted of two females (mean age = 55.00; range 42 to 68) and six males (mean age = 49.00; range 45 to 60).

Instruments

Three instruments were used: the Short Form 36 Health Survey (SF-36; Ware, Snow, & Kosinski, 2000); the PSE-Syndrome-Test (PSE-Test; Schomerus, Weissenborn, Hamster, Rückert, & Hecker, 1999); and the National Adult Reading Test (NART; Nelson & Willison, 1991).

Short Form 36 Health Survey (SF-36)

The SF-36 is a generic measure of health status that assesses the main physical and mental health dimensions affected by illness, disease and treatment. The 36 items in the Survey were drawn from a 245-item questionnaire used in the Rand Medical Outcomes Study (Tarlov et al., 1989). Eight dimensions are assessed: physical functioning; role limitations due to physical health; bodily pain; social functioning; general mental health; role limitations due to emotional problems; vitality energy or fatigue; and general health perceptions. The SF-36 also has two summary scores: physical component summary (PCS) and mental component summary (MCS). The Australian Bureau of Statistics (ABS, 1997) detailed the relationships between the eight dimensions and the Survey's 36 items and also sets

out the Australian SF-36 norms derived from respondents to the 1995 National Health Survey.

The SF-36 is a self-report survey and is mainly in Likert format with a small number of Yes/No questions. An Excel scoring format was developed to perform the calculations required by the Manuals: recalibrate responses as necessary, sum the scores for each dimension, and transform and standardise these to T-scores. These were additionally converted to the two component summary scores by use of factor weights given by the ABS. The Excel scoring format was checked by use of a data set provided by the SF-36 publisher, QualityMetric.

Reliability coefficients for the instrument fall in the range of $r = .70$ to $r = .90$ and a large range of validation strategies are reported in the Manual. The SF-36 is the most used behavioural measure in contemporary medicine according to Kaplan and Saccuzzo (1997) and has been used extensively in HCV research (Forton, Thomas, & Taylor-Robinson, 2003).

PSE-Syndrome-Test (PSE-Test)

The PSE-Test was developed as a paper and pencil test battery for the quantitative assessment of neuropsychological disturbances caused by liver dysfunction. The Manual also commends the test for the assessment of cerebral functions in other illnesses and pharmacological studies. It assesses fine motor control, attention, concentration, visuo-constructive abilities and short-term memory. The PSE-Test includes five sub-tests that have been considered in detail previously. These are the Digit Symbol Test, the Number Connection Tests A and B, Serial Dotting and the Line Tracing Test.

The PSE-Test generates a composite score (CS) derived from the sub-tests. Results on each sub-test are compared to relevant age norms and a sub-test score is

awarded from plus one (better than one standard deviation from the mean) to minus three for scores worse than two standard deviations from the mean. The Line Tracing Test has two results, one for time taken, and one for errors made. Thus, there are six scores for any one participant. The scores are summed to give the CS and this has a possible range from plus 6 to minus 18. The normal range is plus 6 to minus 4 and scores worse than minus 4 are considered pathological.

The instrument was recommended for use in studies of mHE by the consensus group formed at the 11th World Congresses of Gastroenterology (Ferenci et al., 2002). Test-retest reliability coefficients quoted in the Manual are between $r = .56$ and $r = .95$. This is a German test that has not been used in Australia before. The test forms were translated into English for this study. The Manual is currently being translated into English by Swets Test Services.

National Adult Reading Test (NART)

The NART assesses pre-morbid intelligence. The subject is presented with irregularly spelled words such as 'naïve' and is asked to read them. The scoring is based on correct pronunciation. Spreen and Strauss (1998) noted reliability estimates of over $r = .90$ and correlations with IQ measures in the moderate to high range ($r = .4$ to $r = .8$). The administration followed the procedures from Beardsall and Brayne (1990) in that 25 words were administered first and the second 25 words were only administered if the participant correctly pronounced 21 or more of the first 25 words. Scoring also followed the Beardsall and Brayne procedures. The Borana Index was used to assess pre-morbid intelligence for participants who did not receive most of their education in English. Scoring in these cases was in accordance with the computational worksheet provided by Spreen and Strauss 1998 (p. 47).

Procedure

Ethics approval for the study was obtained from Edith Cowan University Ethics Committee and the Hollywood Private Hospital Research Ethics Committee.

Potential control group participants were contacted by telephone and patients were sent a letter inviting participation (Appendix E). For the people indicating a willingness to participate, an appointment was arranged and a confirmation letter (Appendix F) and Information Sheet (Appendix G) were mailed, provided an address was available. Most of the control group were tested in a quiet office at the School of Psychology at Edith Cowan University, Joondalup and most of the patients were tested at the Hollywood Private Hospital Specialist Centre. A small number of the participants chose to have the tests administered at their homes, but in all cases testing conditions were good.

Prior to test administration, all participants were advised of the nature of the study, the voluntary nature of participation, that they were allowed to withdraw at any time, and in the case of patients, that their participation in the study would not adversely affect their medical care. The Information Sheet was discussed and any questions were answered. An Informed Consent (Appendix H) was then completed and signed. When the participants were relaxed and settled the SF-36 was administered, followed by the PSE-Test and then the NART. After the testing session, time was allowed for discussion. The participants were thanked, and it was ensured that each participant left with a copy of the Information Sheet on which were found various contact details.

Scoring of the instruments was according to the manuals and statistical analyses were performed with SPSS Version 11.0 (Appendix I).

Results

Data Screening

The accuracy of data input was confirmed by comparing data sheet totals with mean totals from SPSS Descriptives. Prior to analyses participants' responses on the SF-36, PSE-Test and the NART were examined through various SPSS programmes for missing values and fit between their distributions and the assumptions of univariate and multivariate analyses. No missing values were found and no univariate outliers were detected using the criterion of plus or minus 3 standard deviations from the mean. There were no multivariate outliers using the criterion of each participant having a Mahalanobis distance of less than the critical value for χ^2 at 18*df*, $p < .001$ (42.312).

Assessment of Instruments for Use in Western Australia

To ensure the tests were performing satisfactorily in the Western Australian environment and in the hands of the researcher, comparisons of the control group's results were made with various norms and other studies. The use of T-scores was recommended by Ware and Kosinski (2001) to simplify comparisons.

SF-36

As shown in Table 2 the control group's results (unadjusted for age or sex) were slightly higher than those of a healthy Australian normative group. However, two factors bring the columns to near equivalence. The healthy Australian normative group was older and exclusions were made only for serious physical conditions (ABS, 1997, p. 37). The composition of the control group excluded those with mental as well as physical conditions. The age effect is illustrated by the differences shown in Table 2 between the norms for Australians aged between 35 and 44 years, and those between 45 and 54 years.

Table 2

SF-36 Mean T-scores[a] for Control Group and Australian Norms

	Healthy Controls (n = 13)	Healthy[b] Australian (n = 9922)	Australian[c] Age Group (n = 4110)	Australian[c] Age Group (n = 3104)
Age (years)	37.54	44.37[d]	35 to 44	45 to 54
Scale Scores				
Physical functioning	54.97	52.56	52.25	49.93
Role physical	55.66	52.45	51.38	50.44
Bodily pain	55.26	53.04	51.03	49.70
General health	56.21	53.33	51.47	49.99
Vitality	55.32	52.74	50.37	50.67
Social functioning	54.12	52.17	50.51	50.60
Role emotional	52.04	51.59	50.47	50.47
Mental health	56.00	51.90	49.60	50.13
Component Scores				
Physical	55.53	53.06	52.28	49.90
Mental	53.89	51.66	49.42	50.57

Note. [a] T-score (M = 50, SD = 10) transformations have been calculated with norms and component score coefficients from ABS (1997, p. 31), and as recommended by Ware and Kosinski (2001). [b] ABS (p. 21). [c] ABS (p. 11). [d] Calculated from ABS (p. 35).

PSE-Test

Table 3 shows that the PSE-Test performed as expected with the exception of the Line Tracing Errors sub-test. The data in this Table has not been age or sex adjusted and so a small advantage in favour of the control group could be expected compared with the two healthy older groups in the German studies. In relation to the German norms, the university sourced control group performed better, but in this case IQ would almost certainly account for the differences. Thus, five sub-test scores were comparable with German data.

However, for the Line Tracing Error score the control group scored dramatically better than the comparative groups and as can be seen from the age adjusted T-scores in Table 5, the study groups have done equally well on this test. There is clearly something different in relation to this sub-test, between the Western Australian study and the German data. As each of the study groups have similar results on this sub-test, comparisons between the groups should not be affected. Nevertheless, the matter is currently being reviewed and details are in the Discussion.

NART

The control group had a mean IQ equivalent of 116. This is at the 85th percentile of the general population which is an acceptable result for university students and comparable with the two groups of mainly skilled and professional people whose median scores were 117 and 115 on the NART in the study by Forton, Thomas et al. (2002).

Table 3

PSE-Syndrome-Test Mean Results for Control Group and German Studies

	Healthy Controls (n = 13)	Study[a] Group (n = 22)	Study[b] Group (n = 52)	German[c] Norms (--)[d]
Mean Age (years)	37.54	41.00	44.40	38.00
IQ Equivalent	116.00	--[d]	--[d]	100[e]
Sub Tests				
Digit Symbol	57.54	56.30	54.60	52.00
NCTA (s)	22.31	27.30	28.10	29.00
NCTB (s)	53.77	57.50	58.60	70.00
Serial Dotting (s)	34.15	38.00	36.30	40.00
Line Tracing Time (s)	64.54	71.90	69.30	58.00
Line Tracing Errors	3.77	36.10	38.50	36.00
Composite Score	2.46	1.00	1.05	0.00

Note. [a] Weissenborn, Heidenreich et al. (2001). [b] Weissenborn et al. (2003). [c] Schomerus et al. 1999; [d] Not available. [e] Assumed.

Group Comparisons

SF-36

Table 4 presents the SF-36 scale and component summary scores (PCS and MCS) for the three study groups. Results were transformed to T-scores by using the relevant age and sex means and standard deviations provided by C. Gordon of the ABS (personal communication, 18 July, 2003). This age and sex adjustment was necessary because of the difficulty of matching the control group with HCV-positive groups on these variables.

As the component scores were derived from the scale scores, only the component summary scores were tested for group differences. A one-way multivariate analysis of variance (MANOVA) was performed on the two dependent variables of PCS and MCS. The independent variable was group (HCV status). Using the Pillai's Trace criterion, the combined DVs were significantly affected by group, $F(4,58) = 2.74$, $p = .037$. Post hoc comparisons using the Tukey HSD test revealed significant differences between the healthy controls and the mild HCV group: PCS ($p = .036$), MCS ($p = .035$).

Because the groups were small and unequal and as the assumption of homogeneity was violated for the DV of MCS (Levene test, $p < .05$) the MANOVA results were confirmed by the non parametric Kruskal-Wallis test: PCS ($p = .041$) and MCS ($p = .026$).

Following Bonkovsky and Woolley (1999), and for descriptive comparative purposes, significant Tukey post hoc results ($p < .05$) are asterisked in Table 4.

Table 4

SF-36 Age and Sex Adjusted Mean T-scores[a] for the Study Groups

	Healthy Controls (n = 13)	Mild HCV (n = 11)	Moderate HCV (n = 8)
Female/Male Ratio	5:8	6:5	2:6
IQ Equivalent	116.00	111.55	100.38
Scale Scores			
Physical functioning	53.50	50.41	48.63
Role physical	54.65	45.04*	49.45
Bodily pain	54.31	44.74*	49.78
General health	54.91	39.26*	40.69*
Vitality	54.27	43.61*	47.13
Social functioning	53.58	45.04	49.30
Role emotional	51.13	40.60	50.37
Mental health	55.73	47.90	47.32
Component Scores			
Physical (PCS)	54.10	46.48*	48.03
Mental (MCS)	53.55	43.21*	47.81

Note. [a]T-score (M = 50, SD = 10) transformations were calculated with age and sex means and standard deviations provided by C. Gordon (personal communication 18 July, 2003). Component scores have been calculated with coefficients from ABS (1997, p. 31).
* $p < .05$ compared with healthy control group.

PSE-Test

Table 5 presents the PSE-Test results for the three study groups. The composite score (CS) is the summation of the sub-test scores, the calculation of which was previously described. The sub-test scores have been transformed to T-scores by using the norms relevant to each participant from the Manual (Schomerus, et al., 1999).

The Levene test for homogeneity of variance was not significant ($p > .05$) so a one-way univariate analysis of variance (ANOVA) was performed on the dependent variable CS. The independent variable was group (defined by HCV status). ANOVA was significant, $F(2, 29) = 4.63$, $p = .018$. Tukey HSD post hoc comparisons showed a significant difference between the mild HCV and moderate HCV groups ($p = .013$).

However, ANOVA also showed a significant difference on the DV, IQ Equivalent, $F(2, 29) = 9.0$, $p = .001$. Tukey post hoc comparisons showed significant differences between the healthy control and the moderate HCV group ($p = .001$) and also between the mild HCV group and the moderate HCV group ($p = .018$). A significant Pearson correlation ($r = .616$) was found between the IQ Equivalent and the CS, confirming that the IQ Equivalent was an important covariate. An ANCOVA with the IQ Equivalent as a covariate failed to find a significant difference between the groups on the dependent variable, CS, $F(2,28) = 3.32$, $p = .051$.

Table 5

PSE-Syndrome–Test Age Adjusted Mean T-scores[a] Study Groups

	Healthy Controls (n = 13)	Mild HCV (n = 11)	Moderate HCV (n = 8)
Female/Male Ratio	5:8	6:5	2:6
IQ Equivalent	116.00	111.55	100.38
Sub Tests			
Digit Symbol	54.45	60.86	43.88
NCTA (s)	58.29	62.31	59.55
NCTB (s)	58.77	60.02	45.83
Serial Dotting (s)	60.53	66.00	54.40
Line Tracing Time (s)	47.05	46.40	50.06
Line Tracing Errors	66.14	67.16	65.89
Composite Score (CS)	2.46	3.55	0.75

Note. [a] T-scores (M = 50, SD = 10) transformations were calculated with age means and SDs from the Manual (Schomerus et al., 1999)

Relationship Between PSE-Test and SF-36 Results

As indicated in Table 6 there were no significant Pearson correlations between the CS and the PCS, or the MCS.

Table 6

Correlations Between IQ, CS, PCS, and MCS

Variable	IQ	CS	PCS	MCS
IQ	1.00	.62*	.27	.29
CS	.62*	1.00	.20	.21
PCS	.27	.20	1.00	.29
MCS	.29	.21	.29	1.00

Note. * significantly correlated $p < .01$

Discussion

The first aim of this study was to assess the three test instruments in a West Australian setting and in the hands of this researcher. In line with its excellent reputation, the SF-36 was well accepted by both the university students in the control group, and the HCV-positive patients. As recommended in the Manual the SF-36 was the first test administered and it provided a relaxing and easy start to the testing sessions. The scoring of the mainly Likert-type questionnaire has some intricacies and the Manual recommends the use of computerised scoring systems and in particular, the service provided by the license holder (QualityMetric Incorporated). Unfortunately, this service is not available for use with Australian norms. Because no local scoring system could be accessed the researcher designed a simple Excel system which was thoroughly tested with a data set made available by QualityMetric. In a series of personal communications (M. Kosinski, September, 2003) the question of which norms to use was canvassed. The decision was made to use the Australian norms and scoring algorithms. However, it is worth considering using US norms and algorithms for future Western Australian SF-36 studies in order to provide the opportunity to use the very comprehensive norms and wide range of study data in the two SF-36 Manuals. In this context it is noted that the major normative study in Australia dates back to 1995 and many major instruments, such as the WAIS-III, are used in Australia with US norms. Also, in the case of this current study there were only small differences between the results calculated with Australian algorithms and the results calculated with US algorithms. For example, taking the control group's results and using Australian norm based scoring the PCS was 55.53 (US based = 57.14) and MCS was 53.89 (US based = 54.32). The SF-36

results for the control group in this current study have been very much in line with expectations as discussed in the Results.

The PSE-Test has not been used in Australia, but it was recommended by a well-credentialed consensus group at the 11th World Congresses of Gastroenterology, 1998 (Ferenci et al., 2002). The Licence Holder, Swets Test Services, Frankfurt, gave permission for the test forms to be translated into English and copied, pending the publication of an English version of the Test. English test instructions were provided by one of the test authors (Professor Karin Weissenborn, personal communication, August 4, 2002). The Test was well accepted by the participants who without exception, worked very hard to do well in all the sub-tests. As discussed in the Results an inspection of Table 3 shows that the Test performed as expected with the exception of Line Tracing Errors. There seems to be little doubt that there is something different between this Western Australian administration of the Line Tracing Test and the German administrations. A participant variable could explain part of this fairly unusual result, and all of the participants were conscientious to a fault, however, it is suspected that there is some difference between the English and German versions of the instructions. A small experiment was conducted with one participant using firstly the English instructions as provided, and then repeating the test emphasising more clearly the need for speed as well as the need to make few errors. The participant did the test in 71 seconds with no errors in the first administration, and in the second trial the time taken was 30 seconds with a very low five errors. There would have been a practice effect, but not of the magnitude of the observed difference. This matter is currently under discussion with the senior test author, Professor Weissenborn (personal communications, October 2003). From the viewpoint of the study, the Line Tracing Error results are almost

identical across the three groups so they should not have affected any mean comparisons. However, it is necessary to resolve this matter to achieve international comparability.

The control group performed as expected on the NART with an average IQ equivalent of 116. The Beardsall and Brayne (1990) approach of administering half of the test first and only proceeding to the second half if good results were achieved in the first half, was most appropriate and allowed the test sessions to finish on a pleasing note for all participants.

Overall the tests performed very well. Were they the right choice? The SF-36 is certainly simple, cheap, reliable and valid and the instrument of choice in most recent studies of HCV affected HRQOL. It is hard to find fault with this HRQOL instrument although it has been noted that Forton, Thomas, and Taylor-Robinson (2003) have expressed concern that there is no cognitive function scale. This may be a valid point, but if changes have to be made it would be preferable to add an additional scale rather than seek a new test.

The PSE-Test is simple and cheap to administer and it has been endorsed by a group of leading gastroenterologists after 30 years of experimentation with different measures of mHE. Therefore, this test must be the first choice for research into mHE. It is however, debateable whether the PSE-Test was ideal for use with the healthy control group and the group with mild chronic HCV. Forton, Thomas et al. (2002) suggested that HCV encephalopathy (HCVE) is qualitatively different from mHE. Consequently, they have not used the PSE-Test but have relied on the results from the CDR Battery. It is relevant to note that Córdoba et al. (2003) have used neither the CDR Battery nor the PSE-Test, but have put together yet another battery. Convincing as their study is, there may have been merit in using a tailor-made

cognitive battery for at least one of the experimental groups. If it had been possible it would have been of interest if Córdoba et al. had used the CDR Battery, the PSE-Test and, if considered necessary, additional tests. In the current study a tailor-made test for mHE was used. The PSE–Test does include well-established tests for general cognitive dysfunction, but if the resources had been available it would have been of interest to use the CDR Battery for all groups.

The second goal of this study was to consider the appropriateness of the design. Difficulties have become obvious. Firstly, it is clear that the samples for each group were small and there was no chance of them being at all representative of the populations being studied. This is inevitable with all HCV studies because approximately one third of those with HCV have not yet been diagnosed. However, this current study also emphasised the recruitment of volunteers. The control group was recruited from a pool of university students on a volunteer register and they only participated if it was convenient. As it happened, nearly all of those approached agreed to testing and it is fair to say that a reasonable sample of the more mature university students on the School of Psychology Participant Research Register was obtained. Nevertheless, it could be expected that people who volunteer to be included on such a register are more confident and have better time management than students who do not volunteer.

With the patients who volunteered from the private medical practice, the volunteer effect was almost certainly magnified. The relatively small proportion of patients who were prepared to volunteer can be seen as a confident and competent sub-set of those people attending a particular private practice. But this practice was also found in an upper middle class environment and the consultant is a leading Western Australian gastroenterologist. One could expect that his patients are used to

finding the best solution to their problems and this executive quality is one of those that the PSE-Test is aiming to measure.

It has to be emphasised that volunteer patients from private consulting rooms are almost certainly not representative of people with HCV. But this also means that people who attend outpatient clinics at public hospitals are not representative of diagnosed patients either, and it is these people who are normally recruited for HCV studies.

Another problem with the present study was the impossibility of controlling for the very large range of patient variables. Owing to the private nature of the practice, important variables such as education, occupation, mode of infection, and marital status were not sought. Some of the patients however, did volunteer personal details and it was obvious that there was considerable variability on these factors. In addition, some of the participants mentioned comorbid conditions. All the patients were screened for such conditions and were excluded from the study if the medical consultant believed these comorbidities affected cognitive function. However, other comorbidities might have had an effect on SF-36 scores.

The question of comorbid conditions in HCV research raises considerable concern. The previously cited study by Fontana et al. (2002) illustrated the problem. Of 220 HCV-positive people in the study, from 406 patients invited, 157 (71%) had active psychiatric or physical conditions requiring treatment or monitoring; 33% had depression, 9% anxiety, 40% musculoskeletal problems, 20% cardiovascular, 19% gastroenterological, 17% endocrine, 10% pulmonary, and 13% 'other'. This is not to say that these problems are caused by HCV and Speed (2001) suggested that there are only three accepted non-hepatic manifestations of HCV out of the more than 40 non-liver related diseases that have been linked to HCV. However, whether the

comorbidities are manifestations of HCV or not, the fact remains that these comorbidities are important variables, indeed, so important that Hussain et al. (2001) found the presence of comorbidities to be the most important predictor of HRQOL in CHC patients.

The need for appropriate exclusions, the need to maintain a particularly high standard of privacy and the need for large numbers of participants makes it difficult to see how the current exploratory study design could be extended to full-scale research in the private practice environment. However, longitudinal, repeated measures research with its better control over participant variables, could be practical and meaningful. In fact, there is currently an excellent opportunity to test, by a repeated measures study, the Forton, Thomas et al. (2002) contention that HCV per se causes cognitive dysfunction. At present there is a large backlog of patients waiting for government approval for treatment with ribavirin and pegylated interferon. If such people were tested before treatment and after a sustained viral response (SVR; negative to HCV-RNA six months after treatment completion) then convincing evidence should be obtained about cognitive performance in people with and without the HCV virus. The test battery would include at least the SF-36 and the PSE-Test. The CDR Battery would also be included if it could be practically administered. The addition of neurophysiological measures would complete the picture, but perhaps exceed any practical budget. Such a project may also provide information on minimal hepatic encephalopathy in those with advanced liver disease. This could be feasible because it is well established that fibrosis at Knodell stages 1 to 5 is reversible and there is mounting evidence that cirrhosis is as well. However, there is a problem because it is still not clear how quickly liver damage is reversed after an HCV cure (Friedman, 2003).

Consideration will now be given to the first hypothesis that looked towards a decline in HRQOL at the time of an HCV-positive diagnosis. The current research showed a statistically significant HRQOL reduction in the mild HCV group compared to the healthy controls. This supports the hypothesis and adds to the growing and close to compelling consensus built by the work of Bonkovosky and Woolley (1999), Córdoba et al. (2003), Dunne and Quayle (2001), Foster et al. (1998), Miller et al. (2001), and Rodger et al. (1999).

What happens after many years is not so clear. It is noted that the very small moderate HCV group in the current study had a directional improvement in HRQOL compared to those with less liver damage. This is at variance with the study by Foster et al. (1998) who found a non-significant reduction of HRQOL in people with moderate HCV compared to those with mild HCV. Part of this conflicting evidence could be explained by the preponderance of males (75%) in the moderate HCV study group, because HRQOL is higher in males than females in both Australian and US norms (ABS, 1997, Ware & Kosinski, 2001). Another possible explanation could be that the moderate HCV group may have learned to accommodate their HCV-positive status, or they could have enjoyed a particularly high level of support in a successful transitional process (Glacken et al., 2001). It could be that as HCV progresses there are two processes at play: firstly, a reduction of psychosocial impacts as could be the case with the moderate HCV group; and secondly, an increase of physical symptoms arising from an increasingly damaged liver. The study did not provide strong support for the hypothesis that HRQOL remains constant after the reduction associated with an HCV diagnosis until ChildPugh B/C cirrhosis, but nor did it argue against the hypothesis which has received good support from most authors and most convincingly from the recent work of Córdoba et al. (2003).

The present study did not aim to research the relationship between HRQOL and end-stage HCV, but to complete the HRQOL picture it seems reasonable to accept the Hepatitis C Virus Projections Working Groups (2002) estimate of a reduction in the quality of life of around 68% when jaundice, ascites, gastrointestinal bleeding and psychomotor difficulties are being experienced.

The third hypothesis was that cognitive function deteriorates in people with mild HCV. The study gave no support to this hypothesis. In fact there was a directional improvement in PSE-Test results in the group with mild HCV compared to the healthy controls. This unexpected result contributed to a large difference in PSE-Test results between those with mild and moderate HCV. However, the difference reduced to below significance when an 11.15 percentage point difference in pre-morbid intelligence was factored into the analysis as a covariate. Consequently, the study did not support the fourth hypothesis which looked for a cognitive decline in people with HCV and Child-Pugh A cirrhosis. The numbers in the moderate HCV group and the characteristics of the participants make the findings concerning this fourth hypothesis unhelpful.

Although there were no reportable differences between the groups on PSE-Test scores, there were some important points arising from the study. Firstly, it is interesting to note that only two of the 19 HCV-positive participants scored below their relevant age and sex norm means on the NCTA, a test of attention and motivation among other things. The average was more than one standard deviation better than the age adjusted mean. These results confirm the previous suggestion that the HCV-positive patients were a special sub-group of a special medical practice.

The second point arising from the cognitive testing was that the people with mild HCV performed better, but not significantly better than the university students.

The group means for those with mild HCV would have been even better had the results of one participant (NART score = 96) been deleted. The out-performance of this group is partly explained by the special group effect, but the fact is that the group did exceptionally well and it is hard to believe that they could have done better before they were infected with HCV. It is considered that this adds to the evidence of Forton, Thomas et al. (2002) and Córdoba et al. (2003) that HCV does not affect performance on tests like the PSE-Test. There remains the possibility of HCV-related cognitive abnormalities which are only detectable by neurophysiological techniques and/or computer tests such as the CDR Battery. But the case has not yet been made that results on these tests have a strong relationship to every day living.

The third matter of cognitive note arising from this exploratory study is that only one of the HCV-positive patients had a pathological PSE-Test score result of worse than minus 4. However, that person, whose score was minus 5, had a NART score of 81 so pre-morbid intelligence played a major role in the PSE-Test results. In fact, the participant went about the tests in a rather organised, although slow manner. The participant achieved two scores within the normal range which can be seen as quite an achievement.

This present and other research has found no evidence of cognitive dysfunction in those with mild or moderate HCV. To consider people with compensated cirrhosis it had been hoped to recruit a reasonable number of Child-Pugh A cirrhotics. As this was not possible, little comment can be made on the effects of compensated cirrhosis on cognitive function. On the basis of the full-scale study by Córdoba et al. (2003), it would seem that cognitive dysfunction is not evident in compensated cirrhotics and does not become important until end-stage liver disease.

The fifth hypothesis was that reduced HRQOL is associated with cognitive dysfunction. The hypothesis was based particularly on the work by Groeneweg et al. (1998) who found a strong relationship between cognitive function and quality of life. Their methodology was to diagnose cirrhotics with mHE and then compare the quality of life of cirrhotics with and without mHE. This opportunity was not available in the current study as no one had mHE. Across all participants there were small positive correlations between the PSE-Test composite score (CS) and the SF-36 physical and mental component summary scores (PCS and MCS). These correlations were not significant and therefore the fifth hypothesis was not supported. It would be of interest to reconsider this area of research given a sample with greater variability in PSE-Test results. Such research could be quite difficult because cognitive dysfunction seems to become significant only in people with advanced liver disease (Córdoba et al., 2003). Research undertaken with these people would pose the problem of controlling for major physical symptoms.

In summary, and in relation to the research questions, the evidence from this and other studies, suggests that: a) the SF-36, PSE-Test and NART are all useful instruments and suitable for use in a variety of environments; b) cross-sectional designs are problematic in private medical practice settings; c) HRQOL in people with HCV declines at the time of diagnosis and then stays fairly constant until the serious consequences of advanced liver disease become apparent; d) cognitive function is not greatly affected by HCV until the onset of advanced liver disease; and e) a direct relationship between cognitive declines and HRQOL changes, has yet to be satisfactorily demonstrated.

From a practical point of view it is important for people infected with HCV to be aware that there is no solid evidence that the hepatitis C virus will cause cognitive

dysfunction relevant to everyday living. In addition, the chances are very small of HCV progressing to advanced liver disease and possible cognitive complications. What is even more important is the relevance of this and similar research to anti-viral treatment. This has progressively become more effective since the early 1990s and is likely to continue to improve (Foster, 2002). The offer of treatment, outside of clinical trials, has up until now been based on liver biopsy proof of a reasonable degree of liver damage. The thinking has been that there is little point in subjecting people to unpleasant treatment that may not be successful, unless there are clear indications that the untreated infection will progress to the serious physical consequences of advanced cirrhosis. As observed by Foster, this approach is no longer appropriate, because treatment with ribavirin and pegylated interferon now gives good odds of a cure and the most important issue for the majority of people with HCV infection is the HRQOL decrement resulting from diagnosis. In current health care settings the cost effectiveness of any medical treatment should be justified on the grounds of quality of life years gained (Younossi & Guyatt, 1998). Therefore, the offer of anti viral treatment should be targeted at those people with the greatest current HRQOL decrements as well as those people with an expectation of future lost quality of life.

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Appendix A

Modified Staging: Fibrosis and Cirrhosis (Knodell)

Change	Score
No fibrosis	0
Fibrosis expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging (P-P) as well as portal to central (P-C)	4
Marked bridging (P-P and /or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6

Note. Ishak et al. (1995)

Appendix B

Proposed Nomenclature of HE

HE Type	Nomenclature	Subcategory	Subdivisions
A	Encephalopathy associated with acute liver failure		
B	Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease		
C	Encephalopathy associated with cirrhosis and portal hypertension/or portal-systemic shunts	Episodic HE	Precipitated Spontaneous* Recurrent
		Persistent HE	Mild Severe Treatment-dependent
		Minimal HE	

Note. Ferenci et al. (2002).
*Without recognized precipitating factors

Appendix C

Semiquantitative Grading of Mental State

(West Haven Criteria)

Grade 1	Trivial; lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Note. Ferenci et al. (2002).

Appendix D

Precis - Review of 17 HE Patients

(Summerskill, Davidson, Sherlock, & Steiner, 1956)

The neuropsychiatric complications of these patients had lasted six months to six years. All patients showed sleep disorders, with excessive sleep being an early feature and then an inversion of sleep patterns in some patients. In early to middle stages of the syndrome there was a reduction in spontaneous movements, apathy and general slowness. As dysfunction increased the patients reacted only to intense stimuli and then coma set in. This first resembled normal sleep but deteriorated to foëtal attitudes, rigidity and irregular breathing.

All patients showed various degrees of personality change and six of the patients showed intensification of previous personality trends. Frontal lobe involvement was suggested by the authors with patients being sociable, jocular, unselfconscious and with little drive or initiative when symptoms were at their mildest, but when symptoms were more severe there were cases of incontinence, violence, extreme extroversion, paranoia, childishness, irritability and even of flirting by a Presbyterian minister.

Although mood fluctuated it remained constant in the majority for several days or weeks at a time. Seven of the patients had phases of both depression and euphoria, five showed changes in the direction of euphoria only, four showed changes in the direction of depression only, and one patient had a stable mood that only changed at the height of stupor when she became enraged.

When patients were fully conscious and accessible, their memory for remote events was unimpaired but short-term memory as tested by digit span and three

minute retention methods became progressively impaired. Knowledge of time was disturbed before that of place or identity and spatial orientation was also affected early. Patients would get lost in their own home and be unable to find doors and light switches. Visual agnosia was shown in some patients when semi-conscious, with some urinating in drawers, baths or shoes and one shaving with his toothbrush. Speech was slow and slurred and some had difficulties with trembling lips and the biting of tongues. The presence of visual problems, tremors and poor hand-eye coordination contributed to writing difficulties.

Pyramidal and extrapyramidal elements were evident. The 'flapping' tremor of asterixis was typical, aggravated by fatigue, anxiety or excitement. Intentional movement was disrupted in the more severely affected patients. The unusual combination of muscle rigidity, ankle clonus and flexor plantar was frequently observed. All patients were sensitive to nitrogenous substances and a high protein diet or the administration of ammonium chloride resulted in an increase in neuropsychiatric disturbances. Splenomegaly was found in all patients, as was an extensive portal-systemic collateral circulation.

Appendix E

Invitation to Participate in Study

Letter typed on Professor Reed's Letterhead

Dear

Invitation to Participate in Hepatitis C Research

An Honours student from Edith Cowan University, Mr John Caithness, is currently investigating possible cognitive effects associated with hepatitis C infection. The Hollywood Private Hospital Research Ethics Committee has given approval for this study as have the Ethics Committee of the Faculty of Community Services, Education and Social Sciences of Edith Cowan University.

The purpose of this study is to observe any differences in cognitive function between groups of patients with hepatitis C with various stages of liver damage, by administering specific tests that measure quality of life, fine motor skills, concentration and reading ability. It is expected that these tests will take about 60 minutes of your time. This study may assist in the consideration of appropriate treatment and care of patients with varying stages of chronic hepatitis C and therefore has my support.

If you agree to participate in the study Mr Caithness will contact you by telephone. He will arrange a convenient time and place to administer the tests and send you a letter confirming details and providing more information. Prior to the administration of the tests you will be asked to consider this information more fully, given the opportunity to ask questions, and then asked to complete a Patient Consent Form. To ensure complete confidentiality, you will be allocated a code number that will be used on the test forms and research data. The master list showing your name and allocated code will be maintained in my office under lock and key. Should you wish to find out your results on the tests, which you are very welcome to do, I will discuss them with you. Names will not be reported in the study and should the results be published, participants will not be identifiable.

Whether you participate or not is entirely voluntary. If you do decide to participate then if at any time you wish to withdraw from this study, you are free to do so without prejudice or affecting your current or future medical care. Questions concerning this study can be addressed to myself, or John Caithness, telephone (08) 9284 7834. If you have any concerns about this study please do not hesitate to contact Dr Terry Bayliss, Chairperson, Research Ethics Committee Hollywood Private Hospital, Monash Avenue, Nedlands WA 6009, telephone (08) 9346 6249.

Thank you for considering the contents of this letter. My secretary,
Mrs Sheryle Craven will contact you in a few days to see if you are willing to participate in the study.

Yours sincerely
Professor W. D. Reed

Appendix F

Appointment Confirmation Letter

Typed on Edith Cowan University Letterhead

July 2003

Name
Address
Suburb, WA PC

Dear Name

Hepatitis C Study

We spoke together this afternoon and I am very appreciative of your agreement to participate in our study. I am sure you will find it interesting. Just confirming our arrangements we organised to meet at your place, at the above address, at 9.30am Wednesday 9 July.

As an Honours student from the School of Psychology at ECU I am currently conducting research into the possible cognitive effects associated with hepatitis C infection. Details of the study are in the attached Participant Information Sheet.

When we meet I will ask you to consider the Information Sheet in detail. You will be free to ask me any questions you like and you will then be asked to complete a Consent Form. If you are happy with this, the tests detailed in the Information Sheet will be administered.

Participation is entirely voluntary and if at any time you wish to withdraw from this study, you are free to do so without prejudice or any negative consequences.

Please let me know if you have any questions that arise from this study. My phone number is (08) 9284 7834. If you have any difficulty contacting me feel free to speak to my Supervisor, Dr Elizabeth Kaczmarek on (08) 6304 5193.

Thank you again.

Yours sincerely

_____

Student Researcher
(John Caithness)

Appendix G

Participant Information Sheet

Study Title: Cognitive Changes in Individuals with Chronic Hepatitis C

Investigator: John Caithness

Approvals: The Hollywood Private Hospital Research Ethics Committee has given approval for this study, as has the Research Ethics Committee at Edith Cowan University.

Purpose: To assess any differences in cognitive function between groups of patients with hepatitis C and various degrees of liver damage.

Procedures: Three tests, taking less than 60 minutes in total, will be administered, individually and in private:

1. a paper and pencil test which measures visual orientation, concentration and hand/eye motor speed and accuracy.
2. questionnaire with 36 items about your state of health.
3. a reading ability test requiring the pronunciation of 25 words.

Expected Benefits: While this study is exploratory and small in scale it is expected that it will contribute to the existing body of research on the care of patients with varying stages of chronic hepatitis C. There are no expected personal benefits from participating in this study.

Confidentiality: To ensure confidentiality, you will be allocated a code number that will be used on the test forms and research data. The master list of names and codes for patients at Hollywood Private Hospital will be held under lock and key by Professor Reed. For students from Edith Cowan University the master list will be held under lock and key by Dr Elizabeth Kaczmarek. Names will not be reported in the study and should the results be published, participants will not be identifiable.

Compensation: Your participation will be greatly appreciated, but no monetary compensation will be provided. It is noted that your rights at Australian law do not change upon signing the consent form for this study.

Withdrawal: Participation is entirely voluntary and if at any time you wish to withdraw from this study, you are free to do so without prejudice or any negative consequences, and in the case of patients from Hollywood Private Hospital there will be no affect on your current or future medical care.

Concerns: If you have any concerns about this study please do not hesitate to contact Edith Cowan University's Professor Alison Garton on (08) 6304 5110, or Dr Terry Bayliss, Chairperson, Research Ethics Committee Hollywood Private Hospital, Monash Avenue, Nedlands WA 6009, telephone (08) 9346 6249

Appendix H

Edith Cowan University Participants Consent Form

Typed on Edith Cowan University, School of Psychology, Letterhead

Consent to Participate in Psychological Study

Please read the following statements. Tick (√) the boxes if you agree. The testing procedure will only start if you are happy to tick all of the boxes.

- ☐ I have read the information sheet.
- ☐ I was given adequate opportunity to ask questions.
- ☐ The questions I asked were answered to my satisfaction.
- ☐ I understand the content of the information sheet.
- ☐ I understand the nature of the study.
- ☐ I understand that I am not obliged to participate in the study.
- ☐ I understand that I may refuse to answer questions, refuse to start any tests, or may at any time withdraw from this study.
- ☐ I realise that there will be no negative consequences should I decide not to participate or stop participating.
- ☐ I understand that if this research is published then the participants will not be identified. I consent to such publication.
- ☐ I confirm that I voluntarily chose to complete this questionnaire.

If you have ticked each of these boxes we can proceed to administer the three tests.

Signed at (place)_____

On the _____ day of _____
2003

_____
Signature of participant

_____
Name (Please print)

HOLLYWOOD PRIVATE HOSPITAL
PATIENT CONSENT FORM

TITLE: Cognitive Changes in Individuals with Chronic Hepatitis C

INVESTIGATOR: John Caithness

To be completed by the Participant of the study:

1. Have you read the information sheet about this study? Yes ☐ No ☐
2. Have you had an opportunity to ask questions and discuss this study? Yes ☐ No ☐
3. Have you received satisfactory answers to all your questions? Yes ☐ No ☐
4. Have you received enough information about this study? Yes ☐ No ☐
5. Which Doctor (or other researcher) has spoken to you about this study? _____
6. Do you understand that you are free to withdraw from this study at any time without giving a reason and without affecting your current or future medical care? Yes ☐ No ☐
7. Do you agree to take part in this study? Yes ☐ No ☐
8. Have you received a copy of the information sheet and consent form? Yes ☐ No ☐

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM

_____	_____	_____
Participant's Name	Participant's Signature	Date
_____	_____	_____
Person Obtaining Consent	Signature	Date
_____	_____	_____
Witness Name	Signature	Date

General Linear Model

Statistical Analysis of Data

Between-Subjects Factors

		Value Label	N
GROUP	1	moderate	8
	2	minimal	11
	3	healthy	13

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	.986	997.408[a]	2.000	28.000	.000
	Wilks' Lambda	.014	997.408[a]	2.000	28.000	.000
	Hotelling's Trace	71.243	997.408[a]	2.000	28.000	.000
	Roy's Largest Root	71.243	997.408[a]	2.000	28.000	.000
GROUP	Pillai's Trace	.318	2.737	4.000	58.000	.037
	Wilks' Lambda	.685	2.919[a]	4.000	56.000	.029
	Hotelling's Trace	.457	3.085	4.000	54.000	.023
	Roy's Largest Root	.449	6.518[b]	2.000	29.000	.005

a. Exact statistic

b. The statistic is an upper bound on F that yields a lower bound on the significance level.

c. Design: Intercept+GROUP

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	PCS	384.857[a]	2	192.429	3.836	.033
	MCS	642.894[b]	2	321.447	3.503	.043
Intercept	PCS	75415.494	1	75415.494	1503.540	.000
	MCS	71368.375	1	71368.375	777.762	.000
GROUP	PCS	384.857	2	192.429	3.836	.033
	MCS	642.894	2	321.447	3.503	.043
Error	PCS	1454.600	29	50.159		
	MCS	2661.076	29	91.761		
Total	PCS	81717.504	32			
	MCS	78759.412	32			
Corrected Total	PCS	1839.457	31			
	MCS	3303.970	31			

a. R Squared = .209 (Adjusted R Squared = .155)

b. R Squared = .195 (Adjusted R Squared = .139)

Post Hoc Tests

GROUP

Multiple Comparisons

Dependent Variable		(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.
PCS	Tukey HSD	moderate	minimal	1.5442	3.29085	.886
			healthy	-6.0651	3.18248	.155
		minimal	moderate	-1.5442	3.29085	.886
			healthy	-7.6093*	2.90142	.036
		healthy	moderate	6.0651	3.18248	.155
			minimal	7.6093*	2.90142	.036
	Tamhane	moderate	minimal	1.5442	4.11523	.976
			healthy	-6.0651	3.40686	.298
		minimal	moderate	-1.5442	4.11523	.976
			healthy	-7.6093*	2.72201	.044
		healthy	moderate	6.0651	3.40686	.298
			minimal	7.6093*	2.72201	.044
MCS	Tukey HSD	moderate	minimal	4.5963	4.45108	.563
			healthy	-5.7422	4.30450	.388
		minimal	moderate	-4.5963	4.45108	.563
			healthy	-10.3385*	3.92435	.035
		healthy	moderate	5.7422	4.30450	.388
			minimal	10.3385*	3.92435	.035
	Tamhane	moderate	minimal	4.5963	4.77094	.727
			healthy	-5.7422	2.67136	.140
		minimal	moderate	-4.5963	4.77094	.727
			healthy	-10.3385	4.55999	.119
		healthy	moderate	5.7422	2.67136	.140
			minimal	10.3385	4.55999	.119

Based on observed means.

NPar Tests

Kruskal-Wallis Test

Ranks

	GROUP	N	Mean Rank
PCS	moderate	8	14.38
	minimal	11	12.18
	healthy	13	21.46
	Total	32	
MCS	moderate	8	13.00
	minimal	11	12.64
	healthy	13	21.92
	Total	32	

Test Statistics[a,b]

	PCS	MCS
Chi-Square	6.378	7.324
df	2	2
Asymp. Sig.	.041	.026

a. Kruskal Wallis Test

b. Grouping Variable: GROUP

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
PF	3.077	2	29	.061
RP	17.939	2	29	.000
BP	3.192	2	29	.056
GH	5.375	2	29	.010
VT	5.702	2	29	.008
SF	6.148	2	29	.006
RE	5.908	2	29	.007
MH	4.769	2	29	.016
PCS	2.650	2	29	.088
MCS	10.971	2	29	.000

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
PF	Between Groups	128.484	2	64.242	1.326	.281
	Within Groups	1404.499	29	48.431		
	Total	1532.983	31			
RP	Between Groups	554.646	2	277.323	3.565	.041
	Within Groups	2255.835	29	77.787		
	Total	2810.481	31			
BP	Between Groups	546.128	2	273.064	4.117	.027
	Within Groups	1923.376	29	66.323		
	Total	2469.505	31			
GH	Between Groups	1758.153	2	879.076	9.402	.001
	Within Groups	2711.414	29	93.497		
	Total	4469.567	31			
VT	Between Groups	707.150	2	353.575	4.546	.019
	Within Groups	2255.372	29	77.771		
	Total	2962.521	31			
SF	Between Groups	435.225	2	217.613	2.774	.079
	Within Groups	2274.606	29	78.435		
	Total	2709.831	31			
RE	Between Groups	758.910	2	379.455	2.728	.082
	Within Groups	4033.371	29	139.082		
	Total	4792.282	31			
MH	Between Groups	505.032	2	252.516	3.815	.034
	Within Groups	1919.331	29	66.184		
	Total	2424.364	31			
PCS	Between Groups	384.857	2	192.429	3.836	.033
	Within Groups	1454.600	29	50.159		
	Total	1839.457	31			
MCS	Between Groups	642.894	2	321.447	3.503	.043
	Within Groups	2661.076	29	91.761		
	Total	3303.970	31			

Post Hoc Tests

Multiple Comparisons

Dependent Variable		(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.
PF	Tukey HSD	moderate	minimal	-1.7730	3.23368	.848
			healthy	-4.8683	3.12719	.280
		minimal	moderate	1.7730	3.23368	.848
			healthy	-3.0953	2.85101	.530
		healthy	moderate	4.8683	3.12719	.280
			minimal	3.0953	2.85101	.530
	Tamhane	moderate	minimal	-1.7730	4.26766	.969
			healthy	-4.8683	3.69949	.536
		minimal	moderate	1.7730	4.26766	.969
			healthy	-3.0953	2.42101	.533
		healthy	moderate	4.8683	3.69949	.536
			minimal	3.0953	2.42101	.533
RP	Tukey HSD	moderate	minimal	4.4189	4.09817	.535
			healthy	-5.1967	3.96322	.400
		minimal	moderate	-4.4189	4.09817	.535
			healthy	-9.6156*	3.61320	.033
		healthy	moderate	5.1967	3.96322	.400
			minimal	9.6156*	3.61320	.033
	Tamhane	moderate	minimal	4.4189	5.12189	.784
			healthy	-5.1967	3.43290	.436
		minimal	moderate	-4.4189	5.12189	.784
			healthy	-9.6156	3.80931	.088
		healthy	moderate	5.1967	3.43290	.436
			minimal	9.6156	3.80931	.088
BP	Tukey HSD	moderate	minimal	5.0415	3.78415	.389
			healthy	-4.5313	3.65954	.441
		minimal	moderate	-5.0415	3.78415	.389
			healthy	-9.5727*	3.33634	.020
		healthy	moderate	4.5313	3.65954	.441
			minimal	9.5727*	3.33634	.020
	Tamhane	moderate	minimal	5.0415	4.27205	.587
			healthy	-4.5313	3.51379	.532
		minimal	moderate	-5.0415	4.27205	.587
			healthy	-9.5727*	3.38405	.036
		healthy	moderate	4.5313	3.51379	.532
			minimal	9.5727*	3.38405	.036
GH	Tukey HSD	moderate	minimal	1.4299	4.49298	.946
			healthy	-14.2238*	4.34502	.008
		minimal	moderate	-1.4299	4.49298	.946
			healthy	-15.6536*	3.96129	.001
		healthy	moderate	14.2238*	4.34502	.008
			minimal	15.6536*	3.96129	.001
	Tamhane	moderate	minimal	1.4299	4.50159	.985
			healthy	-14.2238*	2.50434	.000
		minimal	moderate	-1.4299	4.50159	.985
			healthy	-15.6536*	4.67031	.014
		healthy	moderate	14.2238*	2.50434	.000
			minimal	15.6536*	4.67031	.014
VT	Tukey HSD	moderate	minimal	3.5164	4.09775	.670
			healthy	-7.1400	3.96281	.187
		minimal	moderate	-3.5164	4.09775	.670
			healthy	-10.6564*	3.61283	.017
		healthy	moderate	7.1400	3.96281	.187
			minimal	10.6564*	3.61283	.017

Dependent Variable		(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.
VT	Tamhane	moderate	minimal	3.5164	4.64753	.843
			healthy	-7.1400	2.85980	.090
		minimal	moderate	-3.5164	4.64753	.843
			healthy	-10.6564	4.05941	.065
		healthy	moderate	7.1400	2.85980	.090
			minimal	10.6564	4.05941	.065
SF	Tukey HSD	moderate	minimal	4.2627	4.11519	.561
			healthy	-4.2762	3.97967	.537
		minimal	moderate	-4.2627	4.11519	.561
			healthy	-8.5389	3.62820	.064
		healthy	moderate	4.2762	3.97967	.537
			minimal	8.5389	3.62820	.064
	Tamhane	moderate	minimal	4.2627	4.63948	.751
			healthy	-4.2762	3.28532	.525
		minimal	moderate	-4.2627	4.63948	.751
			healthy	-8.5389	3.92370	.137
		healthy	moderate	4.2762	3.28532	.525
			minimal	8.5389	3.92370	.137
RE	Tukey HSD	moderate	minimal	9.7642	5.47987	.193
			healthy	-.7589	5.29942	.989
		minimal	moderate	-9.7642	5.47987	.193
			healthy	-10.5231	4.83140	.092
		healthy	moderate	.7589	5.29942	.989
			minimal	10.5231	4.83140	.092
	Tamhane	moderate	minimal	9.7642	5.89823	.310
			healthy	-.7589	4.37527	.998
		minimal	moderate	-9.7642	5.89823	.310
			healthy	-10.5231	5.24008	.176
		healthy	moderate	.7589	4.37527	.998
			minimal	10.5231	5.24008	.176
MH	Tukey HSD	moderate	minimal	-.5751	3.78017	.987
			healthy	-8.4095	3.65569	.072
		minimal	moderate	.5751	3.78017	.987
			healthy	-7.8344	3.33283	.065
		healthy	moderate	8.4095	3.65569	.072
			minimal	7.8344	3.33283	.065
	Tamhane	moderate	minimal	-.5751	4.49439	.999
			healthy	-8.4095	3.40208	.101
		minimal	moderate	.5751	4.49439	.999
			healthy	-7.8344	3.41990	.113
		healthy	moderate	8.4095	3.40208	.101
			minimal	7.8344	3.41990	.113
PCS	Tukey HSD	moderate	minimal	1.5442	3.29085	.886
			healthy	-6.0651	3.18248	.155
		minimal	moderate	-1.5442	3.29085	.886
			healthy	-7.6093*	2.90142	.036
		healthy	moderate	6.0651	3.18248	.155
			minimal	7.6093*	2.90142	.036
	Tamhane	moderate	minimal	1.5442	4.11523	.976
			healthy	-6.0651	3.40686	.298
		minimal	moderate	-1.5442	4.11523	.976
			healthy	-7.6093*	2.72201	.044
		healthy	moderate	6.0651	3.40686	.298
			minimal	7.6093*	2.72201	.044

Multiple Comparisons

Dependent Variable		(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.
MCS	Tukey HSD	moderate	minimal	4.5962	4.45108	.563
			healthy	-5.7422	4.30450	.388
		minimal	moderate	-4.5962	4.45108	.563
			healthy	-10.3385*	3.92435	.035
		healthy	moderate	5.7422	4.30450	.388
			minimal	10.3385*	3.92435	.035
	Tamhane	moderate	minimal	4.5962	4.77094	.727
			healthy	-5.7422	2.67136	.140
		minimal	moderate	-4.5962	4.77094	.727
			healthy	-10.3385	4.55999	.119
		healthy	moderate	5.7422	2.67136	.140
			minimal	10.3385	4.55999	.119

ANOVA

PHES

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	36.261	2	18.130	4.634	.018
Within Groups	113.458	29	3.912		
Total	149.719	31			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: PHES
Tukey HSD

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
moderate	minimal	-2.7955*	.91908	.013	-5.0653	-.5256
	healthy	-1.7115	.88882	.150	-3.9066	.4835
minimal	moderate	2.7955*	.91908	.013	.5256	5.0653
	healthy	1.0839	.81032	.386	-.9173	3.0851
healthy	moderate	1.7115	.88882	.150	-.4835	3.9066
	minimal	-1.0839	.81032	.386	-3.0851	.9173

*. The mean difference is significant at the .05 level.

Homogeneous Subsets

PHES

Tukey HSD[a,b]

GROUP	N	Subset for alpha = .05	
		1	2
moderate	8	.7500	
healthy	13	2.4615	2.4615
minimal	11		3.5455
Sig.		.141	.440

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 10.245.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

Oneway

Test of Homogeneity of Variances

NART

Levene Statistic	df1	df2	Sig.
2.521	2	29	.098

ANOVA

NART

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1225.273	2	612.636	8.997	.001
Within Groups	1974.602	29	68.090		
Total	3199.875	31			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: NART
Tukey HSD

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
moderate	minimal	-11.1705*	3.83421	.018	-20.6396	-1.7013
	healthy	-15.6250*	3.70795	.001	-24.7823	-6.4677
minimal	moderate	11.1705*	3.83421	.018	1.7013	20.6396
	healthy	-4.4545	3.38048	.397	-12.8031	3.8940
healthy	moderate	15.6250*	3.70795	.001	6.4677	24.7823
	minimal	4.4545	3.38048	.397	-3.8940	12.8031

*. The mean difference is significant at the .05 level.

Homogeneous Subsets

NART

Tukey HSD[a,b]

GROUP	N	Subset for alpha = .05	
		1	2
moderate	8	100.3750	
minimal	11		111.5455
healthy	13		116.0000
Sig.		1.000	.450

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 10.245.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

Correlations

Correlations

		NART	PCS	MCS	PHES
NART	Pearson Correlation	1	.267	.287	.616**
	Sig. (2-tailed)	.	.140	.111	.000
	N	32	32	32	32
PCS	Pearson Correlation	.267	1	.285	.200
	Sig. (2-tailed)	.140	.	.113	.272
	N	32	32	32	32
MCS	Pearson Correlation	.287	.285	1	.213
	Sig. (2-tailed)	.111	.113	.	.243
	N	32	32	32	32
PHES	Pearson Correlation	.616**	.200	.213	1
	Sig. (2-tailed)	.000	.272	.243	.
	N	32	32	32	32

**. Correlation is significant at the 0.01 level (2-tailed).

Univariate Analysis of Variance

Betwcen-Subjects Factors

		Value Label	N
GROUP	1	moderate	8
	2	minimal	11
	3	healthy	13

Tests of Between-Subjects Effects

Dependent Variable: PHES

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	74.693[a]	3	24.898	9.292	.000
Intercept	27.768	1	27.768	10.363	.003
NART	38.432	1	38.432	14.343	.001
GROUP	17.796	2	8.898	3.321	.051
Error	75.026	28	2.680		
Total	335.000	32			
Corrected Total	149.719	31			

a. R Squared = .499 (Adjusted R Squared = .445)