Behavioural Virology Research: The Cognitive and Perceptual-Motor Performance of Chronic Primarily Asymptomatic Hepatitis C Patients

Rowena Hale (B.A., Hon.)

A report submitted as a partial requirement for the degree of Masters of Clinical Psychology in the Department of Psychology, University of Tasmania, 1996.

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Abstract

It is commonly believed that people perform less efficiently when suffering from viral illnesses such as colds or influenza, but there is a scarcity of both conclusive research and replicated data providing scientific evidence for this. The current review gives an appraisal of research into the cognitive effects of viral illnesses and their implications for future research into the hepatitis C virus (HCV), which has been neglected so far in the behavioural virology area. The natural history and aetiology of HCV, including coverage of modes of transmission for chronic and acute HCV and their implications for experimental investigations are also discussed. Finally, there is a summary detailing the importance of behavioural research into HCV and providing suggestions for future studies in the area.

Anyone who has suffered the misfortune of contracting a viral illness would be more than willing to testify to the fact that in addition to their physiological symptoms, they experience adverse effects on mood, behaviour, and cognition. Despite the consistent self-report of performing less efficiently when suffering from viral illnesses, little scientific evidence has been conducted to unequivocally support such claims (Savory, 1992). Particularly in the last decade or two however, an area of research has been developed to begin a thorough investigation into the effects of various viruses on mental functioning and behaviour, it has become known as Behavioural Virology.

With the exception of a minority of individual researchers (Corney, Hale, & Ball, 1994; Perdices, 1994) the majority of behavioural virology studies have been conducted at the MRC Common Cold Unit in the United Kingdom and the Health Psychology Research Unit in Cardiff and Bristol and have involved a range of viruses causing illnesses such as influenza and Infectious Mononucleosis (glandular fever), but not, as yet, HCV. Experimental methods have often involved challenging volunteers with a known virus and then measuring the resulting cognitive-behavioural performance. Up to now, research has found that influenza viruses, common cold viruses, Human Immunodeficiency Virus (HIV), and Epstein-Barr virus (producing glandular fever) affect mental functioning and behaviour in apparently distinct ways, with deficits

ranging from poor attention and concentration to slowed reaction times and motor coordination. Whether or not each individual virus produces a specific and discrete pattern of deficits that is replicable upon retesting however, has yet to be determined.

The causes for these viral induced psychological deficits have not been clearly identified within the literature, however, several possible hypotheses have been proposed. These include that the viruses lead to muscle fatigue resulting in poor performance (Smith, 1993); that the symptomatology of each virus leads to different performance states (Smith, Tyrrell, Coyle & Willman, 1987); that an increase in the release of cytokines such as interleukins (IL-1), tumour necrosis factor (TNF) and alpha interferons by the immune system affects performance (Hart, 1988; Hickie & Lloyd, 1995); and that the infection itself takes a toll on the body's overall reactions (Savory, 1991).

Despite these investigations, research into behavioural virology is only in its infancy and has confined its investigations to a select number of viruses. HCV, which is the virus causing the most concern in Australia at the moment, due to its high endemic rate, has evaded the scrutiny of the behavioural virologist. Interestingly, it shares some common symptomatology with glandular fever (mainly fever, fatigue, and possible liver infection) and could therefore result in a similar profile

of cognitive deficits. One possible reason why HCV has been neglected in behavioural virology research revolves around its association with intravenous (IV) drug use. A large percentage of individuals with HCV are IV users who contracted the virus through shared contaminated needles (Bell, Batey, Farrell, Crewe, Cunningham, & Byth, 1990). IV drug use in participants has been viewed as a confounding factor that would be difficult to control for in experimental research.

Viral hepatitis can be simply described as '. . . inflammation of the liver,' caused by a '. . . tiny, microscopic infectious germ.' (Australian Gastroenterology Institute, 1991, p. 2). Currently, HCV has reached epidemic proportions amongst drug injecting populations in Australia. Bell, Batey, Farrell, Crewe, Cunningham, and Byth (1990) tested the blood of 172 intravenous drug users in South Western Sydney and found that 86% were positive for antibodies to HCV. Other groups showing a high prevalence of HCV compared to community prevalence include haemophiliacs (75.6%), prisoners (30.8%), and female prostitutes (10.4%) (Fairley, Leslie, Nicholson, & Gust, 1990). HCV is more infectious than HIV, and can cause chronic ill health, cirrhosis and liver cancer. The high level of infection ". . . suggests public health authorities face a bigger challenge in controlling its spread than they did with HIV" (Wilson, 1993, p. 1).

The aims of the current review are to provide an accurate definition and detailed outline of HCV, including how both chronic and acute HCV is transmitted through contaminated blood products, transfusions, bodily fluids and person to person contact. This transmission research is further discussed in terms of its implications for experimental investigations. In addition, findings and critical analyses of research into the behavioural effects of other viral illnesses is provided and discussed in terms of their implications for future research into the hepatitis viruses. In conclusion, there is an exploration of the merits behavioural research into HCV would have upon those infected with the virus and the general community as a whole. Recommendations for future investigations into the area are also suggested.

Definitions and Natural History.

Testing is now available for five distinct types of hepatitis viruses (A, B, C, D, and E). However, examination of human stool samples suggest that there is another candidate, hepatitis F and a provisionally designated blood-borne hepatitis G virus. Current investigations suggest the alarming fact that ". . . the hepatitis alphabet may need to be extended even after inclusion of some of these new viruses" (Bowden, Moaven, & Locarnini, 1996, p. 87).

Despite the fact that hepatitis has been recognised as a viral infection since ancient times, there was no immediate evidence for the viral aetiology of hepatitis until the early 1940s. The major difficulties in studying the agent of hepatitis, during a time in which major discoveries in clinical virology occurred were (a) the inability to isolate and propagate the hepatitis viruses in vitro, and (b) a lack of adequate experimental animal models. (Zuckerman & Thomas, 1993).

In regard to the latter point, there were several unsuccessful attempts to transmit hepatitis to non-human primates. Failure was in retrospect, attributed to the fact that many of the animals were already immune to the virus. The first successful transmission of a form of hepatitis infection to chimpanzees did not occur until the early 1970s. As a result, much of the early progress on the hepatitis viruses came from experimental transmission in human volunteers. It was from such studies that they were able to identify "...two antigenically distinct forms of viral hepatitis" (Zuckerman & Thomas, 1993, p. 241).

Hepatitis A or 'infectious hepatitis,' possessed a brief incubation period of two to six weeks and was principally transmitted by the faecal-oral route. In contrast, hepatitis B or 'serum hepatitis,' had an extensive incubation period (six weeks to six months) and the primary transmission route was parenteral.

In 1973, it became apparent that there was a third type of hepatitis that had an incubation period intermediate to that of hepatitis A and B, it was designated non-A, non-B (NANB). Evidence that NANB hepatitis was indeed infectious came from its successful transmission to chimpanzees and the demonstration of serial transmission to other animals. The similarity between humans and chimpanzees in terms of their phylogenetic relationship, immune responses and host-pathogen interactions to a variety of human agents has made chimpanzees extremely suitable for hepatitis research. They are in particular a good model for NANB hepatitis because the development of the host immune response mimics very accurately the clinical and immunological observations in humans. From these studies emerged the discovery in 1989 of the causative agent, it became known as the hepatitis C virus (Choo, Kuo, Weiner, Overby, Bradley, & Houghton, 1989).

HCV is a novel agent, but closely related to both animal pestiviruses (eg. bovine viral diarrhoea and hog cholera) and to the human flaviviruses (eg. yellow fever and dengue fever). It is classified in the Flaviviridae family, but as a separate genus. HCV is now the most common hepatitis virus, affecting about 0.4% (1 in 250) of the Australian community (Australian Gastroenterology Institute, 1991). The mean incubation period of HCV is 10-12 weeks. Clinical diagnosis involves epidemiological history and serological confirmation showing persistent

elevated aminotransferases for at least six months and anti-HCV in the serum.

Acute and Chronic Hepatitis C

HCV can cause acute (short-lived) disease, which may resolve completely. Alternatively, in 50% of patients it leads to chronic hepatitis (greater than six months), with a predisposition towards developing cirrhosis and primary hepatocellular carcinoma (New South Wales Department of Health, 1993).

The onset of acute HCV is insidious, with either quite pronounced symptomatology or no symptoms at all. Malaise, anorexia, nausea, and right upper quadrant pain may be present, and patients may also exhibit abdominal cramps, fever, dark urine, and a general feeling of being unwell (New South Wales Department of Health, 1993). In the 25% in whom jaundice develops, fatigue and anorexia usually worsen. Jaundice can last from a few days to a few months, but is usually less than one month. Some pruritus (violent itching of the skin) may occur, as well as mild weight loss. Fatigue usually abates after the jaundice resolves, but may persist for several months. Abnormal enlargement of liver and spleen are found in a few patients, and arthritis and rashes have also been reported (Zuckerman & Thomas, 1993).

Most patients who go on to develop chronic HCV are either mildly symptomatic or completely asymptomatic. Serum aminotransferases decline from the peaks of the acute phase, but typically remain elevated by two - eight fold. In symptomatic patients, fatigue is the most common complaint, typically accompanied by abdominal discomfort and nausea. With more severe disease, spider angiomata and hepatosplenomegaly may be found. Cirrhosis develops in approximately 20% of chronic patients within ten years. Cirrhosis is when scar tissue forms on the liver and prevents it from working properly. It may be indolent and slowly progressive over a long period, or rapidly progressive. Cirrhosis is often signalled by tiredness, jaundice, fluid retention, bruising, or bleeding. With cirrhosis, weakness, wasting, oedema, and abdominal dropsy are more common (Zuckerman & Thomas, 1993).

When studying the behavioural effects of various viruses, many researchers have failed to mention whether they have taken into account the fact that some patients may be in an acute stage and some the chronic stage of the illness (Smith et al., 1987; Smith, Tyrrell, Al-Nakib, Barrow, Higgins, Leekham, & Trickett, 1989). Length of infection may play a significant role in whether or not deficits exist and the pattern of deficits that are discovered. Not distinguishing groups of participants in the chronic period from those in the acute may result in the failure to determine the deficits unique to each stage, if indeed there are any. Future research investigating

viruses such as HCV needs to clearly delineate which group they are studying (chronic or acute) and analyse and interpret the data for each separately.

Transmission of HCV

Sexual Transmission

It is believed possible that HCV can be transmitted sexually, but it is an inefficient and infrequent means of becoming infected. The prevalence of anti-HCV tends to be higher among sexually promiscuous patients who admit intravenous drug abuse. Researchers looking for HCV in semen have detected it only in a minority of cases. Even when infection is found in two people who are in a sexual relationship, it is not always clear that the route of transmission was necessarily sexual (Tibbs, 1995). Indeed the current evidence for a sexual transmission route is mainly correlational and could therefore be coincidental or a result of some other extraneous factor. HIV could be one of these factors. For example, Eyster, Alter, Aledort, Quan, Hatzakis, and Goedert (1991) found that "The frequency of HCV transmission to sexual partners is five times higher when HIV is also transmitted, suggesting that HIV may be a cofactor for the sexual transmission of HCV" (pp. 764-768).

Maternal-Infant Transmission

A very uncommon but possible route of transmission of HCV is from infected mother to the infant she is carrying. HCV ribonucleic acid (RNA) has been discovered in the serum of newborn babies delivered by women who were anti-HCV positive. This suggests a possible transmission route for HCV (Thaler, Park, & Landers, 1991).

Community Transmission

In some individuals infected with HCV, the only risk factor that can be determined is that they came from a region or community where the virus was fairly rampant. In such cases of community-acquired disease one can only speculate that the virus may be spread by close person to person contact from carriers of HCV. However, general rules of hygiene such as avoiding sharing razors, toothbrushes, and other personal items which may have traces of blood on them, make the risk of transmission very low (Wilson, 1993). Transmission by insect vectors has been proposed but there remains no direct evidence.

Blood Transfusion and Blood Products

HCV is, however, primarily contracted through blood transfusion or blood products that are infected with the virus. The highest prevalences worldwide are found in haemophiliacs, 50-90% of whom are anti-HCV positive. Anti-HCV is also quite common among transplant patients needing frequent blood transfusions, particularly liver, renal, and

bone marrow transplant patients (Baur, Daniel, Pomer, Scheurlen, Opelz, & Roelcke, 1991).

Health care workers also face a small occupational risk of contracting HCV through accidental needle-stick injury. The Hepatitis C Review newsletter (1996), already reports of health care workers who have contracted HCV through needle-stick injury and as a result, are unemployed and ". . . battling for basic workers compensation. . . " (p. 6).

There is also a high incidence of hepatitis C among intravenous drug users (70-92%) due to repeated exposure to carriers of the virus through shared, contaminated needles. One study targeting injecting drug-users in Adelaide, Melbourne, Perth, and Sydney, found that of the 872 users surveyed, 54.8% tested positive for HCV antibodies, whereas only 18.9% reported having HBV and 3.1% as being HIV positive (De La Harpe, 1995).

There is also documented evidence of HCV being transmitted by human bite as a result of saliva containing HCV RNA or saliva containing infected blood (Dusheiko, Smith, & Scheuer, 1990).

Implications from Transmission Studies.

The implication for research into HCV and indeed any hepatitis virus, is the possible confounding variable of IV drug use and concurrent infection with other viruses. It is apparent from the transmission research, that a high percentage of patients infected with HCV are IV drug users. Patients who are continually using IV drugs would have to be screened out of any contemporary experiments, otherwise any real cognition or perceptual-motor performance deficits could be attributed to the effects of drugs like heroin rather than HCV. In contrast, previous IV drug users who have contracted HCV could be allowed to participate, if matched to controls with a similar drug history. Finally, there are patients who in addition to HCV are infected with other viruses such as HIV or Hepatitis B (HBV) because of the risky lifestyle they lead. These patients would also have to be excluded from research, as it would be impossible to attribute any mental performance changes exclusively to HCV.

The Effect of Viral Infections Upon Cognitive and Motor Performance

Behavioural virology research studies the effects of viruses upon cognitive functioning and behaviour. Currently, research has encompassed the influenza viruses, various common cold viruses, HIV, Epstein Barr virus, and

chronic fatigue syndrome, a serious illness possibly arising from a viral infection (Lloyd, Hickie, & Peterson, 1997). The majority have been reported to produce a range of deficits in processes such as attention, reaction time, memory, concentration, and perceptual-motor skills. Just as these viruses have resulted in cognitive decrements, so too could HCV. However, HCV, has been ignored in this area of investigation, despite the virus being a major concern in Australia at present.

Common Cold and Influenza Viruses

Smith, Tyrrell, Barrow, Higgins, Bull, Trickett, and Wilkins (1992) investigated the common cold for pattern sensitivity and contrast sensitivity. In their experiments participants were challenged with Respiratory Syncytial Virus (RSV), Coronavirus, or Rhinovirus. Of those participants who developed a cold after exposure to RSV, they were found to be more sensitive to a visually distracting pattern presented prior to virus challenge than volunteers who did not get a cold. Those who developed a sub-clinical infection reported more illusions after virus challenge than they had done before, whereas uninfected participants and those with colds tended to report fewer illusions on the second test after infection. These effects were not found in participants challenged with Corona- or Rhinovirus. These results suggest that sensitivity to a visually disturbing pattern may be related to susceptibility for developing a cold from the Respiratory Syncytial virus. In addition, subclinical cold

infections (not just clinical illness) can produce behavioural effects.

Smith (1992b) also reports two experiments which looked at the effects of experimentally induced upper respiratory viral infections (cold producing Rhinovirus RV9 and Influenza A/Eng virus) on selective attention. The Stroop task was used to measure attention. There was no effect of either cold or influenza on the speed of carrying out the various conditions involved in the Stroop task. However, participants with influenza illnesses were less accurate at naming colours when distracting colour words were present. These results suggest that the effects of a cold and influenza are different and that an attention demanding task is impaired by influenza.

Four experiments investigated the effects of experimentally induced colds on various aspects of memory of 27, 47, 39, and 30 adults (Smith, Tyrrell, Barrow, Coyle, Higgins, Trickett, & Willman, 1990). Participants were challenged with a Coronavirus or Rhinoviruses RV2, RV9, or RV14. A fully developed cold was found to have no effect upon free recall, digit span, or retrieval from semantic memory performance. However, immediate recognition of important information from a 15 minute story was impaired in participants with colds, which suggests they were less able to follow the theme of the story.

Smith, Thomas, Brockman, Kent, and Nicholson (1993) studied the effects of natural rather than experimentally induced Influenza B on reaction time, repeated numbers detection, free recall, delayed recognition memory, logical reasoning, focused attention, and categorical search. In the first experiment, there were 26 participants with Influenza B, who were tested when they were ill and again when fully recovered. Influenza B had no effect on mood or on performance of the five choice serial response and focused attention tasks and free recall, delayed recognition memory, and logical reasoning tests. However Influenza B patients had significantly longer reaction times compared to when they were free of viral infection, and were slower at repeated numbers detection and less accurate at categorical search. In the second experiment, there were 72 patients with Influenza B. Once again a reaction time effect was found. The Influenza B patients showed a 19% increase in the reaction time for the 10 minute version of the variable fore period simple reaction time test when compared with controls. These findings were in support of Smith et al.'s (1987) earlier findings that Influenza B increased simple reaction time, in their experiment, by 57%.

Finally, Smith et al. (1993) investigated the effects of naturally occurring upper respiratory tract illnesses (URTIs) upon real life work performance. They focussed upon performance efficiency, trying to establish a link between viral infection and the number of workplace

accidents. They studied 923 patients attending Accident and Emergency departments at a time of year when URT viruses were prevalent. There were no significant associations between URTIs and workplace accidents.

Research clearly shows that influenza and the common cold produce different cognitive decrements and, within these broad categories, various strains of each virus also result in distinct impairments. Deficits range from increased reaction time, to significant difficulties in attention, and with the exception of one study (Smith et al., 1993), have been found in naturally occurring and experimentally induced viral illnesses.

Chronic Fatigue Syndrome

Chronic Fatigue Syndrome (CFS) has occasionally been found to be caused by or linked to a viral infection. For some years the Epstein-Barr Virus was thought to be the exclusive cause of CFS, a syndrome characterised by headaches, psychiatric symptoms such as depression, muscle weakness, sleep disturbance, and fatigue for at least six months without identifiable medical or psychiatric cause. This has now been dismissed and CFS has been proposed to be the possible result of imbalances in neurotransmitters; or viral factors in combination, such as retro- and enteroviruses (Lloyd, Hickie & Peterson, 1997). It is included in this review because of its possible viral origins and the effect it has on cognitive functioning.

Smith, Behan, Bell, Millar, and Bakheit (1993) compared 57 CFS sufferers with 19 healthy controls on a number of performance tests. Patients and controls were matched for age and education level. CFS participants were slower on psychomotor tasks (simple reaction time task and 5 choice serial response task), were more visually sensitive than the controls, and were worse at sustaining attention. They were also more distracted by irrelevant stimuli in the Stroop task. In addition, semantic processing and speed of logical reasoning were also impaired, but digit span and free recall performance did not differ significantly from the controls. None of the performance impairments could be attributed to psychopathology.

In support of these findings Daugherty, Henry, Peterson, Swarts, Bastien, and Thomas (1991) report that CFS patients exhibited deficits in attention, motor skills, problem solving, and visual and verbal memory. Smith (1992) then tested the performance of eight CFS patients with 23 controls on pencil and paper performance tasks. CFS patients were slow on a motor task (pegboard task) and performed visual search tasks and working and semantic memory tasks more slowly and less accurately than the controls.

Patients with CFS are slower to react to stimuli. Simple reaction times have been found to be slower than

controls on visual and auditory discrimination tasks (Scheffers, Johnson, Grafman, Dale, & Straus, 1992) and in simple and serial reaction time tasks (Smith, 1991; Smith et al., 1993). Moss-Morris, Petrie, Large and Kydd (1996), in their extensive review of chronic fatigue research, propose that these findings seem to be related to delayed information processing, rather than impaired motor responses. In two studies examining information processing in individuals with CFS and Multiple Sclerosis (MS), results indicated that CSF and MS patients showed significant impairments on tests of complex concentration when compared with appropriate controls and have difficulty on tasks that require simultaneous processing of complex cognitive information (DeLuca, Johnson, & Natelson, 1993; DeLuca, Johnson, Beldowicz, & Natelson, 1995). These studies suggest that CFS patients have a selective impairment in information processing efficiency.

Not all investigators have observed decrements in performance of CFS patients relative to controls. Altay, Abbey, Toner, Salit, Brooker, and Garfinkel (1990) studied controls and CFS patients on a battery of neuropsychological tests and found that CFS patients performed at a significantly higher level than an age-matched group. However, this may have simply reflected the fact that the patients were not matched with controls on educational and achievement records. Studies which have measured the overall intellectual functioning, have found

no evidence of intellectual decline or any primary deficit in intellectual functioning in CFS patients (Scheffers et al., 1992).

There has been no clear evidence of any sensory or perceptual impairments (Prasher, Smith & Findley, 1990; Scheffers et al., 1992), and verbal attention of CFS patients has been found to be comparable with both normative data and matched controls (Moss-Morris et al., 1996). No Magnetic Resonance Imaging or Event Related Potential abnormalities have been found in CFS patients (Scheffers et. al., 1992; Cope, Pernet, Kendall, & David, 1995). Consequently, there is virtually no current evidence revealing that organic factors contribute to any neuropsychological impairment in CFS.

The dilemma with this research is that CFS patients are usually seen many months, if not years, after the supposed original illness. It is therefore problematic to attribute fatigue related symptoms to a preceding viral illness, and it is difficult to determine which virus if any, is actually responsible for the cognitive impairments found in the studies of CFS patients.

Infectious Mononucleosis (IM) or Glandular Fever

Hall and Smith (1993) examined the effects of acute and chronic glandular fever (caused by the Epstein-Barr Virus) on memory, attention, psychomotor performance, and

mood. There was an acute and chronic group of participants and matched healthy controls. Acute IM patients had significantly slower reaction times than controls. Acute patients also had difficulties sustaining attention, making significantly more false alarms in the detection of repeated numbers task than controls. Chronic IM participants were significantly worse than controls at recalling a word list and less accurate on the logical reasoning task, both of which are memory tasks. None of the performance effects could be attributed to depression. The results of this study show selective effects of acute and chronic IM on performance.

Corney, Hale, and Ball (1994) in a study of 16 acute IM patients and 16 matched controls, also found that acute IM participants had significantly slower reaction times than controls (by 28%). They also reported more illusions of movement and colour than controls and were 10% slower at logical reasoning. The logical reasoning scores however were at chance level and therefore probably more accurately reflected a slowed reaction time. Hall and Smith's (1993) findings of interference with attention in acute IM subjects was not replicated however.

In summary, glandular fever has been found to affect memory, attention, and reaction time in chronic and acutely infected patients (Hall & Smith, 1993; Corney, Hale & Ball, 1994). As mentioned previously, HCV, being a virus like glandular fever, may also produce a number of deficits in

cognition. These deficits may be akin to those found in glandular fever patients rather than similar to patients infected with any other virus. The reason for this is that glandular fever affects the human body in similar ways to HCV (e.g. in fever, fatigue and possible liver infection) and therefore HCV may result in similar effects upon cognitive functioning as glandular fever.

Human Immunodeficiency Virus (HIV-1)

HIV attacks and progressively destroys the immune system, having a morbid predilection for the brain. Brain damage can occur as a direct result of HIV infection involving brain cells, or indirectly from tumours or other infections, or infectious processes due to a deteriorating immune system that is increasingly unable to ward of diseases. Asymptomatic HIV type 1 (HIV-1) patients do not tend to shown significant cognitive impairment (Mauri, Sinforiani, Muratori, Zerboni, 1993; Jonnsen, Saykin, Cannon, & Campbell, 1989)). In contrast, symptomatic HIV-1 is characterised by impaired fine motor control, sustained and selective attention, cognitive flexibility, and verbal memory (Maj, Sntx, Janssen, & Zaudig, 1994).

Most of the deleterious effects on cognition and behaviour occur when HIV evolves into Acquired Imunnodeficiency Syndrome (AIDS). Numerous studies have shown that any and every neuropsychological disorder may occur in AIDs patients. These include impairments such as

memory deficits, mental confusion, mild learning and attention deficits, psychomotor slowing, and difficulties with visuospatial processing (Selnes, Galais, Bocellar, & Miller, 1995; Grant, Atkinson, & Hesselink, 1987; Perdices & Cooper, 1989). Eventually AIDS resolves into what has become known as AIDS Dementia Complex. Navia, Jordan, and Price (1986) were the first to describe the progressive cognitive deterioration accompanying AIDS, as AIDS Dementia Complex. It is characterised by forgetfulness, loss of attention, mental slowing, deterioration in executive functioning and later, motor dysfunction (Maruff, Currie, Malone, & McArthur, 1994). The virus causes these deficits by specifically targeting and attacking nervous system tissue and for this reason it is termed a 'neurotropic virus.'

The most recent study in this area that clearly shows how stage of infection (from HIV to AIDS) influences both type and severity of cognitive and behavioural deficits, is Perdices (1994) study of neuropsychological (NP) impairment resulting from HIV-1 infection. Two hundred and eight subjects (Control = 40, Asymptomatic seropositive = 75, AIDS-related complex = 61, AIDS = 33) were given a NP battery which consisted of 51 measures such as memory, motor speed, and reaction time. Based on NP performance after principal component analysis with varimax rotation, five distinct subgroups were detected. The first was a normal performance subgroup, which included the controls. The second consisted of subjects with non-specific subclinical

decrements in performance. The next two groups exhibited impairment consistent with subcortical and frontal cerebral pathology (e.g., impoverished verbal memory and visuomotor coordination) and finally, the last subgroup experienced markedly elevated depression and motor slowing, the latter of which may be the result of clinical depression itself. No other impairments were apparent in this last group.

This study clearly shows that distinct empirically identifiable patterns of impairment exist in patients with HIV-1 infection. However, it would appear that the virus does not produce a homogeneous set of deficits, instead there are substantial variations in patients' impairment between and within particular stages of HIV-1 infection. There was also no significant association between impairment subtype and stage of HIV infection, although participants with normal performance were predominant in the early stages of infection.

Unlike the other viruses previously mentioned, there is no dispute concerning whether or not HIV eventually results in cognitive deficits, not only because of neuropsychological testing and research but because of the scientific knowledge that this virus directly attacks central nervous system tissue.

Possible Biological Mechanisms Underlying Viral Cognitive Deficits

As mentioned, HIV directly invades neural tissue. The demonstration of cognitive deficits in patients with AIDS is therefore not, a great surprise. But how can cognitive impairments in patient groups with infection by viruses that do not directly involve the brain be explained? The causes for these viral induced psychological deficits have not been clearly identified, however, several hypotheses have been proposed. These include that the viruses result in poor performance via muscle fatigue (Smith, 1993); that the symptomatology of each virus leads to different performance states (Smith, Tyrrell, Coyle & Willman, 1987) and that the infection itself takes a general toll on the body's overall reactions (Savory, 1991). None of these theories have been conclusively substantiated by the research. However, one theory has begun to accumulate support over the last decade, and this identifies cytokines as the mediators of immunological and behavioural symptoms and responses in animals infected with viral illness.

Symptoms of acute infections resulting from viruses, such as loss of appetite, hypersomnia, social withdrawal, depressed mood, and impaired concentration and attention, collectively referred to as 'sickness behaviour,' have been shown to be associated with the action of cytokines such as interferons, tumour necrosis factor (TNF) and interleukins (IL-1) within the Cental Nervous System (Hart, 1988).

Investigation of the neuroimmunological and behavioural profiles of sick animals in response to viral infection (Hart, 1988; Dantzer, Bluthe, Kent & Kelly, 1992) has illustrated that infective disorders result in a specific pattern of responses, physiological (increased core body temperature, decreased plasma iron and zinc, increased slow-wave sleep and weight loss) and behavioural (anorexia, decreased psychomotor activity, social withdrawal etc). The stereotyped nature of such responses and their similarities across species suggest that they are mediated by common mechanisms. Research has identified that cytokines such as interleukins (IL-1), TNF and interferons (alpha and gamma) may be this central mechanism. When an animal becomes infected with a virus, cytokines begin to be produced in the periphery of the body via cells from the immune system (e.g. blood monocytes and granular lymphocytes). Once synthesised, they induce a series of central nervous system events which are thought to produce the physiological and behavioural symptoms or 'sickness behaviour' often associated with acute viral infection.

A similar process has been shown to occur in humans. A range of acute viral illnesses (influenza, upper respiratory tract infections and the Epstein-Barr Virus), and chronic conditions such as chronic fatigue syndrome and hepatitis B (Lloyd, Wakefield, & Hickie, 1993) produce viral antigens which in turn result in a cascade of

activation of the cellular components of the immune response, and that cascade appears to be initiated by the release of a variety of cytokines (IL-1, TNF and interferons) which cross the blood-brain barrier. The range of physiological and behavioural symptoms that then occur, such as anorexia, irritability, poor concentration, lethargy and decreased motor activity, seem to be precipitated by the cytokine release.

It has been proposed therefore, that cytokines initially released in the periphery of the human body in response to viral illness may be responsible for the range of physiological and behavioural symptoms (such as lethargy and poor concentration) observed in individuals with infective illnesses (Hart, 1988; Dantzer et al., 1992). Hart (1988) proposes that these symptoms or 'sickness behaviour' form a survival function, allowing the animal to put all its energy reserves and bodily resources into killing off the invading pathogen rather than into muscular activity from the animal moving about.

Further support for the hypothesis that cytokines play a role in the production of physiological and behavioural symptoms during viral infection, comes from interferon research. Exogenous interferon has been given as a form of treatment to hepatitis C patients and carriers of hepatitis B. This treatment has produced symptoms akin to acute viral infection, such as fatigue, impaired concentration, slowness, disorientation, anxiety and depression, but no

organic changes. These symptoms are reversed by stopping the interferon treatment (Smedley, Katrak, Sikora, & Wheeler, 1983; Renault & Hoofnagel, 1989). As the body's immune system naturally produces endogenous interferons when it becomes infected with a virus (Smith, Tyrrell, Coyle & Willman, 1987), researchers propose that just as exogenous interferons produce an exaggerated form of acute viral performance symptoms, so the action of endogenous interferons produces less severe viral symptoms that influence the mental state, causing cognitive deficits such as impaired attention and concentration (Smedley, Katrak, Sikora, & Wheeler, 1983; McDonald, Mann, & Thomas, 1987).

Criticisms of Behavioural Virology Research and Implications for Future HCV Studies

The small sample size inherent in many of the viral research studies leads to questionable reliability of results (Savory, 1992). The majority of infected groups used in these studies are small (Smith et al., 1987). As a consequence, any variations resulting from individual differences could be exaggerated. To some extent this may be compensated for by using analyses of covariance, but the reliability of the analyses on such small groups is questionable. Future research into behavioural virology, including the hepatitis viruses, should aim to increase participant numbers and improve reliability of results. While this is sometimes difficult, due to the small

endemicity rate of some viruses, it should not be difficult with HCV. In 1994 in Southern Tasmania, 189 people were reported as being infected with HCV (Tasmanian Health Department, David Coleman, personal communication, 1995).

Another difficulty with behavioural virology research is that any random sample of participants with a cold or influenza for example, is likely to contain multiple strains and it is difficult to identify the causative virus in a given individual. This makes the studies difficult to compare and may account for some variation in results of studies that are supposedly examining the same viral infection. This is also an issue for any research into HCV, as there are six major genetic groups of HCV and a number of recognised subtypes that are closely related. As mentioned previously, HCV is classified within the Flaviviridae family, however, it comprises a heterogenous group of RNA viruses. Type 4 infection is the most prevalent in Egypt and many parts of the Middle East and Africa, whereas genotypes 1a, 1b, 2a, 2b and 3a are the most prevalent in patients with chronic HCV from countries in Western Europe and the United States. It is therefore important when studying HCV patients, to make sure they are of a common genotype (Dusheiko, Khakoo, Soni, & Grellier, 1996).

Many of the studies on behavioural virology omit mention of whether or not they took into account the

severity of their participants' illness when considering cognitive performance (Smith et al., 1992). Often the symptomatology present is recorded but there is no reference to any analyses of results that compares the impact of symptom severity on task performance. This oversight may lead to real deficits being undetected in participants who may be more severely incapacitated with a virus because they are included with a majority of participants who are relatively well functioning. In principle, at least, this problem can be overcome in hepatitis research by separating the symptomatic from the asymptomatic patients and separately analysing and comparing their data. The importance of determining symptom severity and separating symptomatic from asymptomatic patients is apparent in HIV research, which has shown asymptomatic patients to be relatively cognitively unimpaired (Mouri, Sinforiani, Muratori, & Zerboni, 1993; Jonnson, Saykin, Cannon, & Campbell, 1989), but symptomatic patients to show significant cognitive deficits (Maj et al., 1994).

In addition, it is unclear in many of the viral studies whether or not the control and experimental groups were matched for gender and age (Smith, 1992), and whether there were equal numbers of each sex in the groups. Research suggests that age (Smith & Brewer, 1985) and gender (Gulian & Thomas, 1986) may be important in influencing performance under certain conditions and should therefore be controlled. In Smith et al.'s (1987) study of

Influenza B, any differences in performance on some tests could have been influenced by the imbalance of gender in the control and experimental groups. For example, the experimental group consisted of three infected females, and the control group consisted of two females and five males. Future viral research should ensure that experimental and control groups have equal proportions of males and females, and that they are matched for age.

It is also important when studying the behavioural effects of viruses to screen participants for depression. Often in response to diagnosis or in response to ongoing illness, a reactive form of depression can occur. Depression has been found to interfere with cognitive functioning. For example, it has been found to cause concentration and attention problems in cognitive tasks (Mialet, Pope, & Yurgelun-Todd, 1996). It is therefore important either to screen out potential HCV participants who have accompanying depression or to statistically control for this confounding variable, as the effects of this disorder may obscure the effects of HCV.

Many viral infections result in the patient being prescribed treatment medication, and yet some behavioural virology researchers fail to mention whether they screened subjects for medication use (Perdices, 1994). The effects of medication may make it difficult to determine whether any deficits in performance are due to the virus or the treatment. Future viral research, such as HCV studies,

should take this into account and/or exclude participants on medication. Alpha Interferon (AI), is the medication used to treat a minority of chronic HCV patients. It tends to produce long-term remissions in only 10-25% of patients. Generally, 4-8 hours after initial treatment, an influenza-like condition of fever, chills, anorexia, nausea, sleep disturbance, and fatigue occurs, but this lessens with subsequent injections. AI has been reported to produce stable cognitive deficits such as mental torpor, short term memory difficulty, and reduction in concentration (Renault & Hoofnagle, 1989, in Zuckerman & Thomas, 1993). Treatment is therefore a potential confounding variable, hampering determination of whether any deficits identified would be due to HCV itself. However, as AI is only given to a small percentage of patients with definite liver damage and is an expensive treatment, sufficient unmedicated chronic HCV patients should still be available to research, thus avoiding any possible confounding effects of treatment.

The issue of fatigue is also important in behavioural virology research, particularly in relation to HCV, where fatigue is often a reported symptom. It is often difficult to determine whether any deficits identified in research are due to cognitive slowing or physical fatigue, as a result of the virus. Counterbalancing the order of test presentation can overcome this problem, but few viral studies have reported whether they follow this procedure. Future research would benefit from both counterbalancing tasks as well as attaining a pure measure of motor fatigue

by administering a specific task at the beginning and end of each test session, such as simple reaction time, and determining if there was any motor slowing throughout the session.

Conclusions

It is a commonly held belief that when suffering from a viral infection, individuals perform less efficiently. Gradually, research has been gathered that tends to generally support such claims and illustrate that there are clear deficits in memory, attention, reaction time, motor coordination, perception, and other skills during the course of infection by particular viruses. The majority of viral illnesses studied have been shown to produce some form of deficit, and therefore it is likely that hepatitis C being itself a viral illness, would also produce one or more deficits in cognitive performance. In addition, glandular fever patients during both the chronic and acute stage of the illness have exhibited deficits in memory, attention, and reaction time. As this virus shares some common symptoms with HCV, it is also quite possible that any deficits identified will be similar to those found in glandular fever patients.

A crucial aspect of the care of patients with HCV is general advice, knowledge, and counselling. HCV has received considerable media attention in recent years and

as a result, many people may harbour misconceptions about the nature of the disease. One of the most important issues for patients diagnosed with HCV therefore is appropriate education and support: "...they require accurate information and emotional support to help them come to terms with their diagnosis." (Wilson, 1993, p. 4) All clients should be provided with basic information and counselling, including knowledge about the natural course of the illness, duration, how HCV is transmitted, behaviour change which can prevent the spread of HCV, and what HCV is and its possible effects, both physiological and cognitive. The latter can only be determined through extensive research into the virus.

Investigation into HCV will help determine for example whether or not patients are likely to suffer from any ill effects upon memory, attention, reaction time, and so forth, which in turn have implications for their ability to safely perform tasks utilising those skills, such as driving, studying, and occupational efficiency. In particular, reaction time, attention, and tracking skills which have been shown to be affected by viral illnesses such as glandular fever, are needed to operate and keep vehicles on the road, handle occupational machinery and monitor sources of information such as road signs and pedestrians.

Any deficits in mental performance and behaviour discovered as a result of HCV investigations also have the

potential for being a valuable contributor to any prevention or harm reduction education campaigns. Just as informing people of possible physiological effects of the disease (liver infection and cancer) often make people more careful to avoid engaging in 'at risk' behaviours for contracting the disease (ie. not sharing needles, covering cuts and wounds and practicing safer sex), likewise, informing the public of possible cognitive deficits may have a similar impact.

The merit of research into viral illness is clearly valuable in terms of community education and prevention, for learning more about the virus, its effects and implications for those infected. However, HCV, more prevalent than HIV or AIDS at the moment in Australia has been overlooked in terms of its effect on behaviour and cognition. Patients are in need of knowledge concerning their illness, its effects and prognoses, yet before this can be provided there needs to be some extensive changes in experimental design. Studies into behavioural virology have been subject to numerous methodological weaknesses in the past. Recommendations for design improvement include having controls matched for sex and age, and clearly delineating experimental groups in terms of symptom severity and stage of illness (chronic versus acute) so that any deficits within the infected group are not overlooked. Participants must also be screened for depression, medication, and coexisting illnesses, all of which could interfere with findings. Finally, there needs

to be an increase in participant numbers in order to obtain more reliable results and increased statistical power.

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Behavioural Virology Research: The Cognitive and Perceptual-Motor Performance of Chronic Primarily Asymptomatic Hepatitis C Patients

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Journal Article

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Abstract

This study examined the effects of chronic primarily asymptomatic hepatitis C (HCV) upon cognition and perceptual-motor skills. A battery of six performance tasks measuring concentration, reaction time, hand-eye coordination and attention were given to 12 HCV patients and 12 controls matched for age, sex, and intravenous drug history (if applicable). The hypothesis that HCV participants would exhibit performance deficits as have the majority of viruses currently investigated and that like glandular fever patients, with whom they share some commonalities, these deficits would be slowed reaction time, impaired attention, and memory was generally supported. A series of ANOVAs revealed that HCV participants had significantly slower reaction times that could not be attributed to fatigue alone, and impaired perceptual-motor skills as measured by a Pursuit task. Both these tasks also tap into sustained attention. However, no decreases in memory performance were detected. Implications of the findings for safety, patient counselling, education, and future investigations were discussed.

Viral hepatitis can be simply described as ". . . inflammation of the liver. . . ," caused by a ". . . tiny microscopic infectious germ." (Australian Gastroenterology Institute, 1991, p.2). Of all the hepatitis viruses, viral hepatitis C (HCV), is the most common disease and a major global public health problem. HCV is a novel agent, closely related to both animal pestiviruses (e.g., bovine viral diarrhoea and hog cholera) and to the human flaviviruses (e.g., yellow fever and dengue fever). It is classified in the Flaviviridae family, but as a separate genus. HCV is now the most common hepatitis virus, affecting about 0.4% (1 in 250) of the Australian community (Australian Gastroenterology Institute, 1991). HCV can cause acute (short-lived) disease, which may resolve completely, but in 50% of patients leads to chronic hepatitis (greater than 6 months) (Zuckerman & Thomas, 1993).

It is commonly believed that people perform less efficiently when suffering from viral illnesses such as HCV. However, in contrast to the well studied and documented physiological effects of viruses, little research has been conducted to rigorously examine any possible effects of viruses on cognition or mental functioning (Savory, 1992). In addition, the investigations that have been conducted have focussed on only a select number of viral infections.

The common cold, Human Immunodeficiency Virus (HIV), influenza, and Infectious Mononucleosis (IM or glandular

fever) viruses have been studied in terms of their effects on aspects of human performance, such as memory, attention, and speed of reaction. So far however, the hepatitis viruses, including HCV have avoided the scrutiny of the investigator's eye. One possible reason why HCV has been neglected in behavioural virology research revolves around its association with intravenous (IV) drug use. A large percentage of individuals with HCV are IV users who contracted the virus through shared contaminated needles (Bell, Batey, Farrel, Crewe, Cunningham, & Byth, 1990). IV drug use in participants has been viewed as a confounding factor that would be difficult, but not impossible, to control for in experimental research.

Currently research has found that the majority of the viruses studied produce cognitive deficits. Participants infected with common cold viruses, mainly Respiratory Syncytial Virus, Coronavirus, and Rhinovirus have been found to be more sensitive to a visually distracting pattern, report more illusions, and show impaired attention compared to controls (Smith, Tyrrell, Barrow, Higgins, Bull, Trickett, & Wilkins, 1992; and Smith 1992). Research into participants who were challenged with and then developed infection from Coronavirus or Rhinoviruses RV2, RV9, or RV14, found that the immediate recognition of important information from a 15 minute story was impaired, suggesting they were less able to follow the theme of a story. Influenza B has also been found to produce significantly longer reaction times (Smith, Thomas,

Brockman, Kent, & Nicholson, 1993; Smith, Tyrrell, Al-Nakib, Barrow, Higgins, Leekam, & Trickett, 1987), with slower repeated numbers detection and reduced accuracy at categoric search (Smith et al., 1993).

Likewise, symptomatic HIV-1, a virus that directly attacks the immune system and the brain, has produced its own pattern of deficits, these range from impoverished verbal memory and visuomotor coordination to motor slowing (Maj, Sntx, Janssen, & Zaudig, 1994). When HIV resolves into AIDS these neuropsychological deficits increase to encompass impairments in memory, learning, attention, visuospatial processing, and psychomotor performance (Selnes, Galais, Bocellar, & Miller, 1995).

Chronic Fatigue Syndrome can be included in the behavioural virology research area because it has possible viral origins, such as Retro or Enteroviruses (Lloyd, Hickie, & Peterson, 1995). Its effects on cognition have been reported to be slowed psychomotor responses, and impaired semantic processing and logical reasoning (Smith, Behan, Bell, Millar, & Bakheit, 1993), deficits in attention, motor skills, memory, and problem solving (Daugherty, Henry, Peterson, Swarts, Bastein, & Thomas, 1991; Smith 1992). As CFS patients are usually seen many months, if not years, after the original illness, it is problematic however to attribute the fatigue related symptoms to a preceding viral illness and to determine what if any virus is responsible for any cognitive impairments.

Each of these viral illnesses has resulted in a range of performance deficits which have provided empirical support to self reported decreases in performance efficiency during viral illnesses. It is probable therefore that HCV would also result in measurable performance decrements. Interestingly HCV shares some common symptomatology with glandular fever, mainly fatigue, fever, and possible liver infection. As acute IM participants have shown significantly slower reaction times, difficulties in sustaining attention (Hall & Smith, 1993; Corney, Hale, & Ball, 1994), and chronic IM patients have exhibited memory deficits and lowered accuracy in a logical reasoning task when compared to controls (Hall & Smith, 1993), it is plausible that HCV may result in a similar profile of cognitive deficits as those produced by glandular fever.

The causes for these viral psychological deficits have not been clearly identified within the literature, however, several psychomotor hypotheses have been proposed. These include that the viruses lead to muscle fatigue resulting in poor performance (Smith, 1993); that the particular symptomatology of each virus leads to different performance states (Smith et al., 1987); that cytokines such as alpha interferon and interleukins released by the immune system affect performance (Hart, 1988: Dantzer, Bluthe, Kent, & Kelly, 1992); and that the infection itself takes a toll on the body's overall reaction (Savory, 1991). To date, no

theory has been unequivocally substantiated by the research in question.

The difficulty when embarking into research on the cognitive effects of HCV, is to avoid the numerous methodological flaws inherent in behavioural virology research. Savory (1992) has criticised small sample sizes (as low as 3) which have led to questionable reliability of results (Smith et al., 1987) and experimental and control groups often not matched for gender and age (Smith et al., 1987). Some researchers fail to mention whether they screened participants for medication which can be prescribed for viral infections (Perdices, 1994). Length of illness (acute or chronic) and symptom severity (symptomatic or asymptomatic) has also tended to be overlooked and researchers have failed to delineate groups based upon these criteria (Smith et al., 1987; Smith et al., 1989). All these extraneous factors may have resulted in real deficits going undetected. Finally, fatigue has not been sufficiently taken into account. It is possible that rather than any specific cognitive deficits, patients with a viral illness may be suffering general fatigue which in turn results in poor performance.

There is clearly a case for a study to establish whether, like glandular fever, HCV impairs cognitive and perceptual-motor functioning, and if so, what the profile of impairments is. In the present study, the performance of two groups of participants, 12 HCV patients and 12

controls was compared on a single battery of cognitive and perceptual-motor tasks. All HCV participants were in the chronic stage of the illness (an acute group could not be obtained) and were primarily asymptomatic, but reporting mild symptomatology in common with glandular fever patients, such as fatigue. HCV patients and controls were matched for age, sex, and drug history. To eliminate any confounding variables, all participants were screened for depression, medication, and other viral infections. The design permitted comparisons between groups, and consisted of a battery of performance tasks including tests of memory, reaction time, concentration, attention, and perceptual-motor skills. It was predicted that HCV patients would exhibit a profile of cognitive performance deficits as have sufferers from the majority of viruses studied and that like glandular fever, with which HCV shares some symptomatology, these deficits would consist of significantly slower reaction times, poor attention, and memory deficits in patients when compared to controls.

Method

Participants

Participants were 24 volunteers, 4 males and 8 females, infected with chronic, primarily asymptomatic HCV, and 4 male and 8 female uninfected controls. Twenty other volunteers were excluded from the study due to continued IV

drug use and other concurrent viral illnesses such as hepatitis B.

Participants were recruited from the southern region of Tasmania via advertising and information provided by General Practitioners and through cooperation with liver specialists. They were matched for sex, age, and level of education. Ages ranged from 22 to 84, with no significant difference in age between controls and HCV participants, $F(1, 22) = .00$, $p = .97$. In addition, there was no significant difference between the mean number of years of education for controls (12.25) and the mean number of years of education for the HCV group (12.17), $F(1, 22) = .007$, $p = .93$.

The four HCV participants who were past intravenous drug users were each matched with a control of similar drug history (drug used, time period of use, years since last injection) who did not have HCV (see Table 1). Based upon screening criteria prior to experimental testing, participants were not believed to be using medication or drugs, were not clinically depressed (all scored '0' on the Beck Depression Inventory, BDI, 1978), and had no other concurrent viral infections, disorders or illnesses. Participants self-reported an absence of visual or auditory impairment.

Table 1

IV Drug History of Control and HCV Participants

HCV participants					Control participants				
Age	Past IV user	Drug used	Yrs. of use	Yrs. since used	Age	Past IV user	Drug used	Yrs. of use	Yrs. since used
82	No	-	-	-	83	No	-	-	-
64	No	-	-	-	64	No	-	-	-
36	No	-	-	-	38	No	-	-	-
38	No	-	-	-	38	No	-	-	-
60	No	-	-	-	58	No	-	-	-
38	No	-	-	-	40	No	-	-	-
50	No	-	-	-	49	No	-	-	-
22	No	-	-	-	23	No	-	-	-
22	Yes	Speed	1	4	23	Yes	Speed	1	4
34	Yes	Speed Heroin	2	11	32	Yes	Speed Heroin	1	10
34	Yes	Speed	1	5	32	Yes	Speed	5	7
25	Yes	Speed Heroin	8	2	28	Yes	Speed Heroin	8	3

Note. Yrs. = Years.

Apparatus

Participants were screened for clinical depression via the Beck Depression Inventory (BDI, 1978). The inventory consists of 21 groups of statements such as:

0 I do not feel sad.

1 I feel sad.

2 I am sad all the time and I can't snap out of it.

3 I am so sad or unhappy that I can't stand it.

Participants select the one statement in each group that describes how they have been feeling for the 'past week, including today.' The BDI produces subscale scores for cognitive-affective and somatic-performance aspects of depression, as well as the more widely used total depression score. All participants in both groups failed to score on the BDI, indicating no self-reported depression.

HCV participants were medically classified as primarily 'asymptomatic' by their general practitioners, but before participation were asked to record on a form if they experienced any psychological or physiological symptoms associated with their chronic HCV. All reported only increased fatigue.

All performance tasks were presented on an IBM Compatible 486 computer with a colour monitor, keyboard and mouse. Subjects were allowed to observe the display from the distance they found most comfortable.

Tasks

The performance tasks were subdivided into three main groups, although some of these tasks could be included in more than one classification:

Psychomotor	Pursuit Rotor, Variable Foreperiod Simple Reaction Time and Choice Reaction Time
Memory	Free Recall and Delayed Recognition
Attention/ Concentration	Stroop Colour-Word Task

Details of these tests follow:

Variable fore-period simple reaction time. Each trial began with a one-second pause during which the screen was clear. A tone then sounded and at a random interval 1-5 seconds later, a circle of 10mm radius was presented on the middle of the monitor and the participant had to press a key as quickly as possible. The next trial then began. If the participant failed to respond to the stimulus within a 1000ms 'timeout' period, the next trial began regardless. The task consisted of 30 trials and mean reaction time was recorded.

Pursuit rotor task. At a speed of 8rpm, a circular target of 10mm radius moved clockwise along a regular path of 60mm radius on the monitor. Participants controlled a white cross-shaped cursor with the computer mouse, attempting to keep the cursor in contact with the target circle. The task lasted one minute and the percentage of time on target was recorded.

Choice reaction-time. On each trial of this task, the participant had to choose and execute the correct response to one out of a number of possible stimuli. There were nine squares forming a three by three matrix on the screen, any one of which could light up red on each trial. For each square there was a corresponding response key on the numeric keypad. When a square lighted up red the participant had to press the corresponding response key as quickly as possible. However, before a square could turn red, the participant had to hold down a 'home key' (number '5') to ensure their hand was always in the same position at the beginning of the trial. The stimulus was presented 500ms after the home key was first pressed. The stimulus remained illuminated until the participant pressed a response key. The number of trials was 56 and 'timeout' for responses occurred at 1000ms. Overall reaction time was measured for how quickly the participant could respond, as well as thinking time (time taken before the finger was lifted from the home key) and

movement time (time taken between lifting the finger from the home key and pressing the response key).

Free recall. Participants were shown a list of 20 words (Appendix A) presented at a rate of one every 2 seconds. At the end of the list, participants were given 30 seconds to write down (in any order) as many words as they could remember. The word list was obtained from the MRC Psycholinguistic Database (Coltheart, 1981). They consisted of one-syllable five-letter nouns which were not capitalised, and possessed familiarity, written frequency, concreteness, imagery, and meaningfulness ratings substantially greater than 0. The number of words correctly recalled was recorded.

Delayed recognition memory. At the completion of the test session, participants were shown 40 randomly ordered words in succession, at the rate of one every 2 seconds. These included the 20 words from the Free Recall task, plus 20 distractors (Appendix A) also taken from the MRC Psycholinguistic Database (Coltheart, 1981). Like the Free Recall words, distractors were five-letter nouns, of one syllable, and possessed similar ratings of familiarity, concreteness, imagery, written frequency, and meaningfulness. The task was to indicate whether or not each word was a member of the previous Free Recall list by pressing, as quickly as possible, the 'S' for same or "D' for different

button on the response board. The percentage of words correctly identified was recorded.

Stroop colour-word task. In this task there were two conditions, in each of which participants were presented with a colour name, centred on the computer screen and displayed in one of ten colours. On the screen, underneath the colour name was a row of four coloured boxes, which were represented by four keys on the keyboard (keys '1,' '2,' '3,' and '4'). In condition 1, participants had to respond only to the word, ignoring the colour of the ink. For example, if the word was 'green', and box number 2 was green, then the subject would press button '2' on the keyboard as quickly as possible. In the second condition, participants responded only to the ink colour, ignoring the word. For example, if the word 'yellow,' was displayed in brown ink, and box number 4 was brown, then the participant would press button '4' on the keyboard as quickly as possible. There were 100 trials presented in four blocks in each condition, with a 50ms delay between trials. The ten colours used were: red, green, white, black, blue, cyan, magenta, yellow, brown and gray. Prior to commencement of this task it was ascertained that all participants could distinguish these colours. Reaction times and number of correct responses were recorded for each condition.

Procedure

Participants completed each performance task once, with the exception of simple reaction time, which was tested both at the outset and at the end of the single experimental session.

At the beginning of the test session, participants were initially given a consent form to complete. A BDI was also completed, as was an information sheet (see Appendix B) which looked at issues such as intravenous drug use and any symptoms HCV participants experienced. In addition, participants signed forms giving the researcher permission to obtain from their General Practitioners, their HCV status, list of medications used, and any other viruses contracted. Participants were then informed that they could take a short break between tasks if they so desired. Test instructions were presented on the computer screen and the tasks were counterbalanced for each subject, with the exception of three. Simple reaction time was always given as the first and last test, as a measure of fatigue, and free recall was always the second test and delayed recognition the second last. The session required approximately 1 hour.

Results

A series of between groups analyses of variance (ANOVAs) (Appendix C) were performed on the raw data (Appendix D) from

each of the six performance tasks. The independent variable included in all the analyses was group (HCV vs Control). Significance levels were $p<.05$ for ANOVAs. A repeated measures analysis of variance was also carried out on HCV and control participants' simple reaction time scores at the beginning and end of the test session.

Free Recall

The between groups ANOVA carried out on the number of words correctly recalled was not statistically significant, $F(1, 22) = .27$, $p = .61$.

Delayed Recognition Memory

The number of correct responses and the average reaction time of correct responses were analysed in two separate ANOVAs. The main effect of group failed to reach significance for the former [$F(1, 22) = 2.15$, $p = .16$] and the latter data [$F(1, 22) = .31$, $p = .58$].

Pursuit Rotor Task

The mean percentage of contact for each group was analysed. The main effect of group reached significance $F(1, 22) = 4.61$, $p = .04$, with Table 2 illustrating that HCV

participants possessed a lower mean percentage of time on target than controls.

Table 2

Mean Percentage of Contact on Target in the Pursuit Rotor Task for HCV and Control Participants

Variable	Label	M	SD	n
Entire Population		49.50	18.51	24
Group	HCV	41.97	17.53	12
Group	Control	57.04	16.87	12

Variable Fore-period Simple Reaction Time

There was no 'timeout' data, as both groups responded to the stimulus within the 500ms period given before the next trial began.

Each group had two reaction time measures, one at the beginning and one at the end of the test session. A repeated measures analysis of variance was carried out on HCV and control participants' simple reaction time scores at the beginning and end of the test session. There was no main

effect for session time, indicating that the first and second reaction time means were not significantly different for both groups, $F(1, 22) = .03$, $p = .86$. The reaction time by group interaction also failed to reach significance, $F(1, 22) = .21$, $p = 65$. There was however, a significant main effect for group, $F(1, 22) = 4.7$, $p = .04$, with Figure 1 illustrating HCV participants have longer reaction times than controls at the beginning and end of the test session.

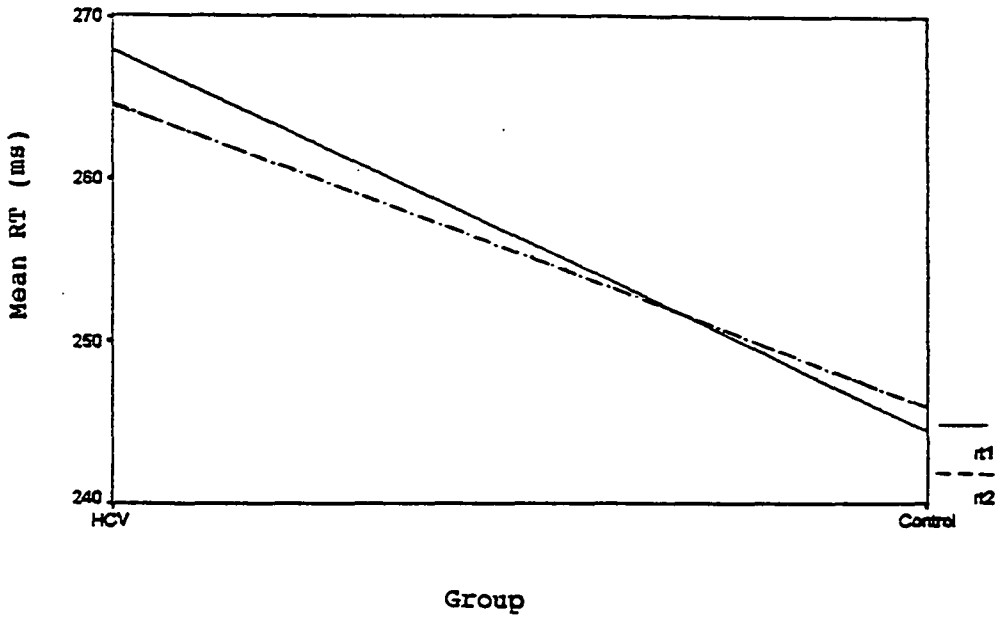

Figure 1. Mean simple reaction times for HCV and control participants at the beginning and completion of the test session.

Stroop Colour-Word Task

Word Condition: An analysis was conducted on the number correct data from the word condition of the Stroop task. The main effect of group failed to reach statistical significance, $F(1, 22) = .10$, $p = .76$. The same analysis was performed on the reaction time data for the word condition. Once again, there were no significant main effects for group, $F(1, 22) = .21$, $p = .65$.

Ink Condition: The mean number correct and reaction time data for the ink condition of the Stroop task was also analysed. In both cases, the main effect of group failed to reach significance [$F(1, 22) = .00$, $p = .99$ and $F(1, 22) = .21$, $p = .65$ respectively].

Choice Reaction Time

Four measures relating to choice reaction time were taken. These included the number of correct responses; mean thinking time; mean moving time; and overall mean reaction time. All were analysed separately using ANOVAs. There were no significant main effects for group [$F(1, 22) = .63$, $p = .44$; $F(1, 22) = 2.58$, $p = .12$; $F(1, 22) = .46$, $p = .51$; and $F(1, 22) = .29$, $p = .60$].

Discussion

Small but significant differences in simple reaction time and perceptual-motor performance as a function of group (HCV/control) were found in the present research.

HCV participants exhibited longer reaction times and poorer hand-eye coordination as measured in a simple reaction time and pursuit rotor task. Both these tasks involve perceptual, motor, and sustained attention components in order to successfully perform them. These deficits in performance were predicted, as glandular fever patients, with whom hepatitis C patients share some similarities such as fatigue and possible liver infection, have been found to show poor attention and longer reaction times when compared to healthy controls in previous research (Hall & Smith, 1993; Corney, Hale, & Ball, 1994). Whether the cognitive performance deficits were more associated with motor, perceptual or attention aspects of performance (all of which are tapped into by reaction time and pursuit rotor tests), could be examined in future HCV research by the use of tasks which clearly separate these functions. It is important to note however, that attention is not likely to be as much involved, as all other attention tasks such as the Stroop produced non-significant results.

As HCV participants reported increased fatigue during viral infection, any increases in reaction time could be attributable to physical fatigue rather than cognitive

slowing in processes such as attention and perception. In order to determine whether it was the former or latter, reaction time performance was measured at the beginning and end of the test session, on the assumption that fatigue should have more impact on simple reaction time at the end of a one hour series of tests than at the beginning. No significant differences in reaction time between time one and time two were found for either group. This suggests that the longer reaction times of HCV participants may be cognitively based rather than just the greater physical fatigue reported by the HCV participants.

What was perhaps surprising, however, was that reaction time measures during more complex tasks such as the Stroop colour-word task, choice reaction time and delayed recognition test were not significantly subject to HCV infection. This may suggest that it is not motor speed but rather a perceptual or eye-hand coordination factor measured in simple reaction time and pursuit tasks that is compromised in HCV patients, because motor speed is not deleteriously affected in other tasks by HCV.

Unlike Glandular Fever patients, no impairments in memory were found in HCV participants, contrary to expectations. However, though these two viruses share some common symptoms, it is not surprising that they should produce some deficits unique to the particular virus itself.

With the exception of viruses that have been found to directly attack the brain such as HIV, evidence for understanding underlying mechanisms responsible for cognitive performance deficits resulting from viruses such as HCV is lacking. As mentioned previously, several hypotheses have been proposed, ranging from muscle fatigue (Smith, 1993), to the action of cytokines from the immune system (Hart, 1988; Dantzer et al., 1992) and to the body's reaction to the infection itself (Savory, 1991). Further research into the physiological aspects of viral infections is needed to elucidate the precise mechanisms involved.

Whether the profile of deficits exhibited in HCV patients is unique to that virus and is replicable remains to be seen. It is important to recognise that there is a scarcity of replication in the behavioural virology area, resulting in a lack of independent confirmation of research results (Savory, 1992). Generalisations about viruses leading to particular impairments therefore become over simplified and potentially misleading. Certainly, the reliability of the present results would have been more substantial with increased participant numbers as originally planned, but many potential HCV participants had to be excluded due to concurrent viral infections and continuous IV drug use, all of which could have confounded results. Without such exclusions, the scientific value of the study would have been severely compromised. Regardless of this fact, the sample size here nevertheless compares satisfactorily with the number used in the majority of

published studies in behavioural virology (11 in Smith et al., 1987; and 10 in Smith et al., 1989) and was certainly more adequate than the amount sequestered in some previous behavioural virology studies (only 3 were used in Smith et al., 1987).

It would be valuable for future research to compare the performance of a chronic HCV group of patients with that of acute HCV patients. Other viral research has clearly illustrated the importance that the variable stage or length of infection plays upon both the type and severity of cognitive impairments resulting from viral illness (Perdices, 1994). The difficulty with this in HCV research however, is that few individuals realise they have HCV during the acute phase, as the majority are relatively asymptomatic, and this would be a major handicap in recruiting acute HCV patients. Future research may benefit from also looking at different levels of severity of chronic HCV, as some viral studies have shown that symptomatic patients tend to exhibit more extensive and significant deficits (Maj et al., 1994). Due to the limited population in Tasmania it was impossible to recruit a symptomatic chronic HCV group to compare to the primarily asymptomatic patients for the present study. In addition many severely symptomatic chronic patients are receiving interferon treatment which is known to interfere with cognitive functioning (Zuckerman & Thomas, 1993).

Research into the effects of common viruses such as HCV is clearly beginning to provide some support for self reports

by those infected with viruses of decreases in their performance efficiency. While this may appear to be proving the obvious, only objective testing is capable of elucidating the exact nature of performance impairments that patients are bound to find hard to define. The findings of small but significant deficits in primarily simple motor/attention/perception tasks in HCV patients do not necessarily propose a serious risk for occupational safely, and for tasks such as driving which require these skills (keeping the car on the road and monitoring road signs and pedestrians), but it is certainly important that chronic HCV patients be encouraged to be more cautious and alert when engaging in activities that require these skills, especially when they themselves report increased fatigue.

In addition, counsellors of HCV patients, tend to state that in order to come to terms and cope with their diagnosis, patients require accurate information about their illness and its effects, both physiological and psychological (Wilson, 1993). Research such as the present study, can aim towards fulfilling the last of these requests. However, as these results have yet to be replicated and elaborated, assertions that all chronic HCV patients experience impairments in motor/attention skills would be premature and an overgeneralisation, a trap that many studies in the behavioural virology area fall into.

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Appendices

Appendix A Word lists for free recall and delayed recognition tasks.

Appendix B Information sheets completed by participants.

Appendix C ANOVAs on the raw data.

Appendix D Raw data.

Appendix A

Word lists for free recall and delayed recognition tasks.

FREE RECALL	DELAYED RECOGNITION
List A	Distractors for list A
price	floor
reach	start
scene	earth
drive	stand
eight	stock
mouth	trade
glass	cause
claim	month
fight	piece
share	wrong
style	press
dance	truth
break	plant
check	blood
spoke	chief
touch	horse
sight	green
shape	doubt
speed	plane
drink	staff

Appendix B

Information sheets completed by participants.

University of Tasmania

DEPARTMENT OF PSYCHOLOGY
Hepatitis C Research
CONSENT FORM

I consent to participate in a psychological experiment on the effects of chronic Hepatitis C (Hep. C), conducted by Rowena Hale and Peter Ball.

I give permission to have my Hep. C status confirmed by my physician, my intravenous drug history known to the experimenter (if applicable) and to have it confirmed that I am not suffering from any other condition, which could interfere with the research results. I have fully read the information forms that are to be sent to my doctor.

I have been informed that one experimental session is involved, lasting approximately one hour.

I understand that each session will involve participation in reaction time, attention, memory, concentration, reasoning and hand-eye coordination tasks, administered by computer. I understand that my identity and my personal data will be coded and kept confidential by the investigator, and that I may withdraw from the experiment at any stage, without prejudice. I also understand that I may request breaks within each session, if I feel fatigued.

All my questions have been answered and it has been explained to me that I shall be provided with extra details about the nature of the experiment when my participation has been completed. I undertake not to divulge to any probable future participant, information likely to make that person ineligible to take part in this research.

I agree that research data gathered for the study may be published, provided that I cannot be identified as a subject.

Signature of Subject..... Date.....

I have explained this project and the implications of participation to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Signature of Investigator..... Date.....

Subject Number _____

Testing Date _____

Testing Time _____

Subject Information Sheet

Name: (INITIALS ONLY) _____

Contact Number: _____

Gender: M/F Age: _____

Occupation: _____

Years of Education: _____

How is your eyesight? _____

How is your hearing? _____

Have you ever used intravenous drugs, if so, what drugs? _____

Aproximately how many times would you have used intravenous drugs? _____

How long (approximately) since you last injected drugs? _____

Name of a friend/relative who might act as a control? _____

Contact number of friend/relative: _____

Could you please list the name of your GP and where their practice is situated? _____ _____

Have you experienced any physical or psychological symptoms as a result of your infection with Hepatitus C? If so, could you please list them below (eg. jaundice and difficulty concentrating):

_____

_____

_____

_____

Appendix C

ANOVAs on raw data.

* * * A N A L Y S I S O F V A R I A N C E * * *

FREER FreeR
by GROUP Group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	1.500	1	1.500	.274	.606
GROUP	1.500	1	1.500	.274	.606
Explained	1.500	1	1.500	.274	.606
Residual	120.333	22	5.470		
Total	121.833	23	5.297		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

PURROTOR PurRotor
by GROUP Group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	1363.835	1	1363.835	4.607	.043
GROUP	1363.835	1	1363.835	4.607	.043
Explained	1363.835	1	1363.835	4.607	.043
Residual	6512.754	22	296.034		
Total	7876.589	23	342.460		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * * * * Analysis of Variance -- design 1 * * * * * *

Tests of Between-Subjects Effects.

Tests of Significance for T1 using UNIQUE sums of squares

Source of Variation	SS	DF	MS	F	Sig of F
WITHIN+RESIDUAL	24749.88	22	1124.99		
GROUP	5304.61	1	5304.61	4.72	.041

* * * * * * Analysis of Variance -- design 1 * * * * * *

Tests involving 'RT' Within-Subject Effect.

Tests of Significance for T2 using UNIQUE sums of squares

Source of Variation	SS	DF	MS	F	Sig of F
WITHIN+RESIDUAL	7073.43	22	321.52		
RT	10.45	1	10.45	.03	.859
GROUP BY RT	68.64	1	68.64	.21	.649

* * * A N A L Y S I S O F V A R I A N C E * * *

SCOLCOR SColCor
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	.042	1	.042	.000	.990
GROUP	.042	1	.042	.000	.990
Explained	.042	1	.042	.000	.990
Residual	6045.917	22	274.814		
Total	6045.958	23	262.868		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

SCMEANRT
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	23732.170	1	23732.170	.208	.653
GROUP	23732.170	1	23732.170	.208	.653
Explained	23732.170	1	23732.170	.208	.653
Residual	2515448.549	22	114338.570		
Total	2539180.720	23	110399.162		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

SWORDCOR
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	15.042	1	15.042	.095	.760
GROUP	15.042	1	15.042	.095	.760
Explained	15.042	1	15.042	.095	.760
Residual	3472.583	22	157.845		
Total	3487.625	23	151.636		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

SWMEANRT
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	16758.735	1	16758.735	.213	.649
GROUP	16758.735	1	16758.735	.213	.649
Explained	16758.735	1	16758.735	.213	.649
Residual	1728021.790	22	78546.445		
Total	1744780.525	23	75860.023		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

DRCORR DRCorr
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	54.000	1	54.000	2.152	.157
GROUP	54.000	1	54.000	2.152	.157
Explained	54.000	1	54.000	2.152	.157
Residual	552.000	22	25.091		
Total	606.000	23	26.348		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

DRRT DRrt
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	12064.650	1	12064.650	.312	.582
GROUP	12064.650	1	12064.650	.312	.582
Explained	12064.650	1	12064.650	.312	.582
Residual	851522.559	22	38705.571		
Total	863587.210	23	37547.270		

24 cases were processed.
0 cases (.0 PCT) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

CRTCORR crtcorr
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	108.375	1	108.375	.630	.436
GROUP	108.375	1	108.375	.630	.436
Explained	108.375	1	108.375	.630	.436
Residual	3783.583	22	171.981		
Total	3891.958	23	169.216		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

CRTMEANT crtcorr
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	30455.100	1	30455.100	2.576	.123
GROUP	30455.100	1	30455.100	2.576	.123
Explained	30455.100	1	30455.100	2.576	.123
Residual	260121.967	22	11823.726		
Total	290577.067	23	12633.786		

24 cases were processed.
0 cases (.0 pct) were missing.

[illegible] ANALYSIS OF VARIANCE [illegible]

BY CRTMEANM crtcorr
GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	3939.844	1	3939.844	.456	.506
GROUP	3939.844	1	3939.844	.456	.506
Explained	3939.844	1	3939.844	.456	.506
Residual	189896.216	22	8631.646		
Total	193836.060	23	8427.655		

24 cases were processed.
0 cases (.0 pct) were missing.

* * * A N A L Y S I S O F V A R I A N C E * * *

CRTMEANR crtcorr
by GROUP group

UNIQUE sums of squares
All effects entered simultaneously

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	9243.375	1	9243.375	.293	.594
GROUP	9243.375	1	9243.375	.293	.594
Explained	9243.375	1	9243.375	.293	.594
Residual	694340.998	22	31560.954		
Total	703584.373	23	30590.625		

24 cases were processed.
0 cases (.0 pct) were missing.

Appendix D

Raw data.

Table 1

Pursuit Rotor Raw Data for HCV and Control Participants

Participant	Percentage on Target	
	'HCV'	'Control'
1	37.75%	52.17%
2	20.16%	49.21%
3	37.75%	55.06%
4	45.06%	47.04%
5	65.02%	50.59%
6	22.33%	58.10%
7	65.22%	54.94%
8	49.80%	58.70%
9	20.55%	25.89%
10	35.97%	59.29%
11	34.01%	78.06%
12	69.96%	95.45%

Table 2

Delayed Recall Raw Data for HCV and Control Participants

HCV Participants

Participant	Mean RT	No. Correct
1	984.8	28
2	1012.5	33
3	925.4	26
4	873.3	30
5	832.4	32
6	1263.2	9
7	725.9	28
8	747.4	28
9	897.8	29
10	847.7	30
11	619.5	25
12	980.2	26

Controls

Participant	Mean RT	No. Correct
1	937.9	26
2	748.9	30
3	1147.6	28
4	820.4	31
5	983.6	33
6	1484.0	28
7	829.1	32
8	855.6	26
9	854.4	37
10	1107.2	32
11	854.8	25
12	624.7	32

Table 3

Simple Reaction Time Raw Data for HCV and Control Participants

Participant	Mean RT 1		Mean RT 2	
	'HCV'	'Control'	'HCV'	'Control'
1	246.3	212.3	251.9	210.6
2	335.1	230.6	300.4	225.2
3	285.6	227.3	263.7	212.0
4	234.5	291.1	238.0	261.8
5	283.8	252.7	274.6	266.8
6	249.2	242.1	278.5	251.4
7	282.3	263.6	314.8	252.6
8	269.0	252.8	259.5	234.5
9	258.3	247.1	241.7	237.97
10	258.1	267.4	276.5	281.9
11	221.5	223.4	215.9	252.8
12	291.1	223.4	223.4	263.7

Table 4

Free Recall Raw Data for HCV and Control Participants

Participant	Number of Words Recalled	
	'HCV'	'Control'
1	3	4
2	8	8
3	7	4
4	10	6
5	9	7
6	2	2
7	4	6
8	7	5
9	3	6
10	8	8
11	4	5
12	9	7

Table 5

Stroop Raw Data for HCV and Control Participants

HCV partcipants

Participant	Word condition		Ink condition	
	Correct	Mean RT	Correct	Mean RT
1	87	1540.1	96	1346.6
2	84	1870.3	63	1871.7
3	88	1484.7	98	1241.9
4	100	977.3	98	871.5
5	98	1156.0	96	848.6
6	69	2115.3	61	2056.3
7	100	1167.8	97	1004.9
8	93	1432.2	99	867.4
9	91	1377.4	94	1113.6
10	97	1286.1	100	945.2
11	90	1374.8	86	1298.4
12	97	1106.8	97	1073.9

Control participants

Subject	Word condition		Ink condition	
	Correct	Mean RT	Correct	Mean RT
1	86	1563.6	82	1241.1
2	96	1351.4	95	1304.2
3	93	1615.1	98	1251.2
4	94	1247.7	94	993.0
5	94	1343.8	99	916.7
6	42	1862.3	31	1880.7
7	97	1215.1	97	1097.3
8	97	1280.4	98	834.7
9	95	1302.2	94	1015.9
10	96	1316.8	97	1208.3
11	87	1004.2	89	1119.2
12	98	1146.97	100	922.95

Table 6

Choice Reaction Time Raw Data for HCV and Control Participants

HCV participants

Subject	Correct	Av. thinking time	Av. Moving time	Av. RT
1	35	422.3	411.9	801.9
2	32	557.8	365.6	923.4
3	43	494.3	321.96	803.4
4	56	251.0	323.7	574.7
5	46	392.8	129.0	524.2
6	37	449.9	230.1	680.0
7	15	626.3	135.3	747.0
8	49	329.6	241.5	566.1
9	52	595.7	202.8	798.5
10	25	487.7	263.6	751.2
11	52	514.3	184.9	699.2
12	55	299.6	95.9	395.5

Control participants

Subject	Correct	Av. thinking time	Av. moving time	Av. RT
1	28	435.4	183.1	613.9
2	53	416.6	280.9	697.5
3	53	432.1	273.6	561.6
4	48	374.3	218.5	592.7
5	54	349.96	222.7	565.6
6	16	448.7	356.8	805.5
7	54	480.0	178.1	658.1
8	29	496.2	56.8	537.8
9	51	156.1	345.7	501.8
10	53	311.9	180.3	492.3
11	53	313.96	150.3	464.2
12	56	251.1	152.0	403.1

Note. Av. = Average.