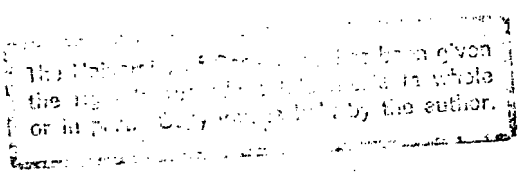
UNIVERSITY OF CAPE TOWN
DEPARTMENT OF PSYCHOLOGY

THE EFFECTS OF PIRACETAM ON PSYCHOMETRIC PERFORMANCE IN CHRONIC ALCOHOLICS

A THESIS SUBMITTED TO THE DEPARTMENT OF PSYCHOLOGY, UNIVERSITY OF CAPE TOWN, IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ARTS IN PSYCHOLOGY.

ANTHONY EDWARD PRICE, B.A. (UCT), B.A.(HONS) (UCT)

RONDEBOSCH, SOUTH AFRICA
OCTOBER, 1984.



ACKNOWLEDGEMENTS

I wish to express my appreciation to Dr Raphael Hassoun and UCB for the financial support which made this study possible, and to the patients and staff of William Slater Hospital for their willing co-operation.

Individual acknowledgements are due to Professor Peter du Preez, Department of Psychology, University of Cape Town, for undertaking supervision of this study; to Dr Ashley Robins, Department of Pharmacology, University of Cape Town, for his advice and facilitation of the study in all its stages; to Francis Hemp for her guidence in the selection of psychometric instruments; to Mark Forshaw for statistical advice; to Alex Reynolds for technical assistance; and to Bea Dorrington for administrative assistance.

ABSTRACT

A randomised, placebo-controlled double-blind crossover design was employed in assessing the effects of piracetam treatment on the functional capacities of abstinent chronic alcoholics.

A sample of 63 subjects, selected for reliability (to counteract an anticipated high drop-out rate) and for a minimum period of abstinence from problem drinking of three months was drawn from the William Slater Hospital, Rondebosch and commenced the trial. The trial consisted of two 8-week periods, with daily dosages of 4,8gm of piracetam or placebo. Subjects were assessed on a psychometric battery yielding a total of 31 scores at baseline, crossover (8 weeks) and trial termination (16 weeks). The final sample size was 48 after drop-outs and non-compliance had been taken into account. Scoring of test data for these subjects was completed before breaking protocols. Results were analysed by means of two way analysis of variance with repeated measures on the trials variable.

Only two of the 31 analyses yielded significant differences between piracetam and the placebo. These yielded opposed results, and as this number of significant results could be expected due to chance alone, it was concluded that they were probably chance results and that no differences existed between the effects of piracetam and placebo on the functional capacities of chronic alcoholics.

TABLE OF CONTENTS

RESULTS

LIST OF TABLES

LIST OF FIGURES

1. CHRONIC ALCOHOLISM

1.1 TRENDS IN THE STUDY OF ALCOHOLISM

To date a large portion of the studies on chronic alcoholism have concentrated on personality and demographic variables and drinking typologies. However, excessive long-term alcohol consumption has also been regularly associated with neurological and neuropsychological complications. Withdrawal of alcohol frequently results in states of epilepsy, delirium tremens and hallucinosis, while interactions of alcohol and vitamin deficiencies are considered to cause Wernicke's encephalopathy, Korsakoff's psychosis, polyneuropathy (including peripheral neuropathy) and pellagra (Ron, 1977). Several of these conditions can be fatal. Lesser complications include ataxia, nystagmus and tremor (Rix, 1983).

Early studies of the chronic effects of alcohol on the brain concentrated around the Wernicke-Korsakoff psycho-syndrome, very probably due to its clearly defined symptomatology. A factor contributing to the limited interest shown in this field was undoubtedly the seeming intactness of the majority of chronic alcoholics when measured on indices of overall intellectual functioning (eg - FitzHugh et al., 1960; Grant et al., 1979; Ron, 1982), while diagnosed brain damaged populations were regularly reported as exhibiting marked deficits on performance sub-tests of the more commonly used intelligence tests (FitzHugh et al., 1960, 1965; Anastasi, 1968).

Memory impairments have been the most commonly reported deficits in chronic alcoholics who do not exhibit signs of the Wernicke-Korsakoff psycho-syndrome, the earliest of these reports dating back to the nineteenth century. With the advent of neuropsychological test batteries in the last thirty years specifically designed to assess subtle changes in functional capacities, more evidence of functional impairment has

been uncovered. Further, neuropathological and neuroradiological studies, the latter made possible by recent technical advances, have provided a steadily mounting body of information indicative of morphological abnormalities in the brains of chronic alcoholics.

With these advances interest was at first shown in changes in the cerebellum. Nystagmus, ataxia and tremor are frequent consequences of cerebellar damage (Rix, 1983). However, such was the extent and variety of the impairments found in chronic alcoholics that cerebellar damage could not account for more than a portion of this (Lynch, 1960). Lishman (1981) now feels that the bulk of emphasis of study has shifted to the cerebrum. As yet the less clinically marked morphological and functional abnormalities of chronic alcoholism are only imperfectly understood.

1.2 THE EFFECTS OF ALCOHOLISM ON THE BRAIN

1.2.1 The Contribution of Studies in Neuropathology

Courville (cited in Ron, 1977) studied the effects of alcohol on the central nervous system. He found a high degree of cerebral atrophy which was often widespread, but was more marked in the frontal lobes. Ventricular enlargement was also observed, but this was not as emphasised by Courville. At a microscopic level Courville found cell loss and other abnormalities.

He concluded that dietary deficiencies could not be responsible for the atrophy observed and attributed this to alcohol toxicity. Although Courville did not supply data to support his contention, he asserted that alcohol abuse was the commonest cause of cerebral atrophy between the ages of 40 and 60 years. This implies an argument of increasing vulnerability to alcohol toxicity as a function of age, a contention which has received considerable support in recent years.

Eleven well-nourished alcoholics were studied by Lynch (1960) who compared their brains to those of five matched controls. Lynch found

differences between the two groups in that the alcoholics exhibited a greater degree of diffuse cortical atrophy, although he did not single out the frontal lobes as did Courville. Cortical cell loss was estimated at between 20% and 40% in the alcoholics, taking the conditions of the controls' brains as baseline values.

Lynch also found numerous small lesions in the alcoholics' thalamus, and found their livers both fatty and cirrhotic. Courville had mentioned that much of the cell loss observed had been avascular. Lynch concluded that this implicated the capillary microcirculation which might be severely impeded by repeated fatty emboli originating in the liver condition of the alcoholic group. This contention was supported by the findings of Acker et al.(1982) who found significant positive correlations between degrees of liver and brain damage, and by Kroll et al. (1980) who found liver damage consistently related to moderate cortical atrophy. However, Lynch considered this to be only one of several possible mechanisms and suggested that toxic and anoxic factors, as well as imbalances of metabolites and vitamins, should also be considered.

Harper (1982) studied brain weights of 101 chronic alcoholics, relative to other alcoholics all taken from a routine unselected series of autopsies. These were of interest in that only 21 of the 101 had been diagnosed as experiencing episodes of Wernicke's encephalopathy while alive, although all showed evidence of Wernicke-type lessions in the mammillary bodies and the tissues surrounding the third ventricle, in conjunction with frontal lobe cortical atrophy.

Harper found that brain weights of both the 101 alcoholics exhibiting signs of Wernicke's encephalopathy and other alcoholics in the series were significantly smaller than the brain weights of non-alcoholics. He argued that, as alcoholics without signs of Wernicke's encephalopathy lost approximately the same amount of brain weight, malnutrition which is usually cited as being involved in the aetiology of Wernicke's encephalopathy, could not be responsible for the observed brain lesions

in the undiagnosed cases, and that these lesions were possibly the result of repeated sub-clinical episodes during life. Lishman (1981) took up the argument, proposing that with the now increased consumption of vitamins, alcohol abuse which previously would have resulted in clear cases of Wernicke's encephalopathy, now results in a sub-clinical form of the same disease, characterised by circumscribed cerebral lesions which go unnoticed individually, but which develop stepwise towards structural damage of increasing size. This might present the external appearance of a dementing process.

The common feature of all the above studies is the finding of loss of cerebral cells through atrophy, particularly in the frontal lobes. There is evidence of sub-cortical damage sustained through alcohol abuse, but this appears to occur only in some cases. Harper and Plumberg (1982) in a related study to Harper's (1982) study, concluded that ventricular enlargement, a measure used to assess atrophy of a central nature, is an inaccurate marker of cerebral atrophy. From this body of evidence the only safe conclusion to be drawn is that chronic alcoholism results in cerebral atrophy, especially in the frontal lobes. There is also a suggestion of damage to arousal regulating areas such as the thalamus and the mammillary bodies, although functional reduction in arousal should not necessarily be taken as proof of such damage because arousal is a joint function of both the cortex and subcortex (Maloney & Ward, 1976; Lezak, 1976).

1.2.2 The contribution of Neuroradiological Studies

The greatest contribution to the increased understanding of morphological changes associated with chronic alcohol abuse comes from studies utilising the Pneumoencephalogram (PEG) and Computerised Axial Tomography (CAT). Whereas prior to their advent the only study directly investigating these changes was neuropathological, it is now possible to investigate these changes in living subjects.

The PEG was the first of these instruments to be developed and involves injecting air into the subarachnoid spaces. Its application

causes considerable discomfort ot patients and thus it has not been used on non-clinical (ie - normal) populations (Ron, 1977). Consequently, only other clinical populations can be used as controls.

The CAT scan is a modern and non-invasive procedure which is safe and eminently suitable for both research and clinical purposes. As a diagnostic instrument it has superseded the PEG nowadays in routine practice.

1.2.2.1 Pneumoencephalographic Studies:

Tumarkin et al. (cited in Ron, 1977) used the PEG on a group of seven US servicemen referred for assessment because of declining work performance associated with alcohol abuse. This was a very young group relative to most alcoholism research, with a mean age of 32 years and a mean reported drinking history of 11 years. Despite their youth all subjects were found to exhibit cortical atrophy, and four also had ventricular enlargements. As Tumarkin et al. had excluded all other probable aetiologies beforehand, the only interpretation possible was that the observed changes were due to alcohol abuse.

In a controlled study using schizophrenics as controls, Haug (cited in Ron, 1977) assessed chronic alcoholics between two and four weeks after the disappearance of delirium tremens following withdrawal of alcohol. Of the alcoholic subjects 74% exhibited cerebral atrophy, compared to only 8% of the schizophrenic sample, a statistically significant difference. A positive correlation was found between length of drinking history and presence and severity of cerebral atrophy.

Brewer and Perrett (cited in Ron, 1977) assessed a group of 33 subjects described as 'alcoholics' and 'heavy social

drinkers' with a mean age of 50 years. The authors excluded persons over 60 years of age and any cases where brain damage might be ascribed to other aetiologies, and several days were allowed to elapse so as to avoid contamination due to acute effects of alcohol. Cortical atrophy was found in 30 subjects, in 28 of whom frontal atrophy was present and of these, 19 exhibited additional atrophy in the parietal lobes.

The above studies may be criticised on several grounds, the most notable of which is the method of scoring the PEG. This is usually a rating and can thus be substantially contaminated. The absence of control groups in two studies also makes the conclusions drawn appear weaker. Nevertheless, Ron (1977) in her review concluded, on the basis of many more studies, that findings repeatedly reflected cortical and subcortical atrophy, the former frequently involving the frontal lobes.

1.2.2.2 Computerised Axial Tomographic Studies:

Fox et al. (1976) compared the scans of 12 alcoholic subjects to 60 scans reported to be normal. Ages of the alcoholic subjects ranged from 34 years to 64 years, so in the absence of a reported mean age, it may be concluded that these subjects probably represented a 'middle aged' alcoholic population. As a result, neurological abnormalities should be expected to be more common than in younger subjects, due to normal degenerative processes.

The alcoholic group represented a selected series, chosen for scanning because of symptoms of neurological disease. Taken in conjunction with the previous point, this argues for caution in generalising from this study. The findings, however, statistically differentiate between the groups, marked ventricular enlargement being observed in 8 alcoholic subjects, but in only one control subject.

The findings of this study should be regarded as merely suggestive of ventricular enlargement due to the effects of alcohol abuse, possibly combined with idiosyncratic factors. Interestingly, Fox et al. also found liver damage in all alcoholic subjects. This study holds no further direct implications for cortical atrophy, however, as scans containing such evidence were excluded from this study.

Studying CAT scans of 60 hospitalised alcoholics constituting an unselected group, Von Gall et al. (1978) found moderate to severe atrophy in 75% of alcoholic subjects, while only 4 alcoholics were totally free of atrophic signs. Cortical atrophy was more common than subcortical atrophy, although there were more 'severe' cases of the latter, in the ratio of 3:2. All alcoholics admitting to a drinking history of more than 20 years were found in the 'moderate atrophy' and 'severe atrophy' classifications, none falling into the 'mild atrophy' classification. Cortical atrophy was found most frequently in the frontal lobes, with decreasing incidence, in order, in the temporal and parietal lobes. Comparing indices of subcortical atrophy (ie - ventricular enlargement) to those of a group of headache sufferers, it was found that these indices were more highly related to age in the alcoholic group, arguing for an increasing vulnerability of subcortical areas to alcohol with advancing age.

Cala et al. (1978) found cerebral atrophy in 19 of their 26 alcoholic subjects (mean age 39,3 years) and found cerebellar atrophy in 16 of the 19 cerebrally atrophied alcoholics. In all, 22 alcoholics exhibited cerebral or cerebellar atrophy, or both. Subjects displaying mild cortical atrophy displayed this alone, while more advanced cortical atrophy was associated with ventricular dilation. Cortical atrophy was diffuse and symmetrical across the hemispheres, but was prominent in the frontal lobes. Significant correlations were found between

degrees of cerebral atrophy and both age and length of drinking history, but these were of minor predictive value.

In a later study utilising a control group of normal volunteers, Cala and Mastaglia (1980) distinguished between alcoholics and heavy social drinkers. They found only 5% of the 240 alcoholics scanned had normal CAT scans, compared to 33% of heavy social drinkers. The control group did not contain the same age range as the other two groups and normative data could only be obtained to the age of 40 years. Nonetheless, the grades of atrophy at comparable ages demonstrated clear differences between normal controls and heavy social drinkers and alcoholics. All groups showed increasing atrophy with age, but controls differed in the extent of these age-related changes, these being much smaller than those observed in the other two groups, which differed between themselves. Alcoholics demonstrated the highest mean grades of atrophy at all but one age bracket.

Subjects with histories implicating possible head injuries from other sources had been excluded to leave alcohol as the only known variable operative. Cortical atrophy was found to be widespread and symmetrical in nature in alcoholics and heavy social drinkers, but again was severest in the frontal lobes.

The authors pointed out that the alcoholic sample constituted a selected sample and that this must temper their findings, but were still forced to conclude that there is a progressive premature shrinkage of the brain in alcoholics. They also noted that heavy social drinkers exhibited significant brain damage without noticeable symptoms.

Similar findings came from Cala et al. (1980) who found pathological degrees of atrophy in alcoholics relative to healthy controls. Alcoholic subjects exhibited global atrophy more often, particular mention, though, being made of the

frontal lobes. The vast majority of alcoholics suffering cortical atrophy also had ventricular enlargement. There were already marked differences between groups in the age range from 20 to 29 years, and age was significantly related to the presence of cortical atrophy in the male, but not the female subjects of either group. Length of drinking history was also found to correlate with cortical atrophy.

In none of the above three studies is it clear as to how abstinent the alcoholic subjects were at the times of assessment.

Lusins and Zimberg (1980) found a significant difference between sub-groups of their alcoholic sample exhibiting or failing to exhibit normal CAT scans as a function of length of drinking history. Age and age of onset of drinking did not relate to CAT scan results. The predominent finding was of cerebral atrophy, although a large minority of subjects exhibited normal scans. Lusins and Zimberg differed from prior studies in using precise linear measurements to define their categories of atrophy, as opposed to rating. As the human brain varies greatly in size and shape, this objective approach, not being related to overall features, can in any individual either over-estimate or under-estimate atrophy. Rating, conversely, is related to overall features, but relies on subjective clinical judgment. These differences can possibly result in varying findings.

Blind rating of CAT scans of alcoholics and matched medical controls was used by Kroll et al. (1980). The alcoholic group was examined for occult brain damage and subjects with medical, neurological or nutritionally suspect histories were excluded. All subjects were under 50 years of age. Results indicated mild to moderate cortical atrophy in 11 of the 16 alcoholic subjects. This result implies that alcoholics, whether they

outwardly exhibit symptoms of neurological abnormalities or not, do in fact, appear to possess such abnormalities. Methodologically the blind rating procedure eliminates the possible influence of sunjective bias in ratings.

Assessments of the occurrence and patterns of development of atrophy in the normal population were made by Bergman et al. (1980). Using official state agencies the authors drew a stratified random sample from the population at large. They found that ventricular enlargement increases in incidence with age to an incidence of 23% in the age bracket from 60 to 65 years (the oldest group in the study). Although they found several significant correlations between incidence and the extent of the various forms of atrophy, these were small and worthless for explanatory purposes.

Eighteen subjects in this sample, loosely described as 'problem drinkers,' were then compared to the rest of the sample. The incidence of central atrophy, ie - ventricular enlargement, was 33% in the 'problem drinker' group compared to 10% in other subjects. Problem drinkers also differed in the incidence of cortical atrophy, about 40% of their number being so classified compared to 14% of other subjects. These findings were supported by the results of a further study comparing alcoholic subjects to normal controls (Bergman et al., 1980). The conclusions went further insofar as the degree of ventricular englargement as a function of age was accelerated in the alcoholic group.

Wilkinson and Carlen (1980) compared neurologically impaired and neurologically unimpaired alcoholics to normal controls. Ventricular widening and sulcal widening (ie - cerebral atrophy) differentiated alcoholics from controls, and severity of cerebral atrophy correlated with age in the neurologically impaired alcoholics, but not in unimpaired alcoholics.

The impaired group included cases of Wernicke's encephalopathy and Korsakoff's psychosis and it was these cases which exhibited the severest abnormalities.

Zelozowiki et al. (1981) took CAT scans of 25 alcoholics who constituted a series of hospital admissions from which all cases exhibiting neurological symptoms of brain damage or any history suggestive of such a possibility were excluded. This sample was predominently male with a mean age of 36,8 years and a mean history of alcohol abuse of 11,4 years. Scanning took place between 2 and 6 weeks after cessation of drinking, thus eliminating the possibility of contamination from acute intoxication. The authors examined ventricular enlargement relative to the two dimensional area of the brain on the CAT scan slice, a method which is less influenced by subjective bias and by the variability of brain size. Scores indicated definite brain damage in 8 subjects, while 23 subjects yielded scores one standard deviation or more above the mean score for the normal population on this index. No assessment of cortical atrophy was attempted. However, another study on a young alcoholic sample (30 years mean age) by Lee et al. (1982) found cerebral atrophy in half of the subjects. These subjects were also abstinent and, once again, selection had eliminated all cases where other aetiologies could have caused brain damage.

A further young alcoholic group of 30 subjects with drinking histories of 10 years were scanned in the first three days of a detoxification programme (Graff-Radford et al., 1982). Eliminating other aetiologies the authors repeated the findings of frequent occurrence of cortical atrophy (18 subjects) and slightly less frequent ventricular enlargement, measured as a ratio of areas (11 subjects). Graff-Radford et al. concluded that, in the light of their own and previous results, it could be concluded that alcoholics developed brain damage at a relatively early age, but also found that length of drinking

history and cortical measures only related systematically in older alcoholics.

Possibly the strongest study to date was that of Ron (1982) who compared 100 alcoholics (mean age 43,5 years) to 50 controls, mostly life-long abstainers. Ron's alcoholic sample appeared neurologically normal and was scanned after the effects of detoxification had subsided, on average, 34 days after the last drink. At initial scanning the alcoholic subjects were inpatients. Ron found that all CAT indices separated alcoholics and controls and that these differences were accentuated by advancing age. All but cerebellar atrophy were postively and significantly correlated with age in the alcoholic group, but age of onset of drinking and duration of drinking history did not correlate with these indices.

What emerges from the above studies is that, even in 'younger' alcoholics, pathological degrees of cortical atrophy and, to a lesser extent, ventricular enlargement are repeatedly reported. Cortical atrophy is most frequently cerebral in nature and tends preferentially to involve the frontal lobes, although the temporal and parietal lobes are also affected. The atrophy is diffuse and symmetrical, showing no lateral preferences.

Although the studies by Ron (1982), Lusins and Zimberg (1980) and Zelozowiki et al. (1981) used data gathered after the acute effects of intoxication should have subsided, other studies might reflect these acute effects rather than more 'long term' effects. Several studies have reported the possibility of a limited degree of reversibility of brain damage.

1.2.3 The Reversibility of Brain Damage in Chronic Alcoholism

Carlen et al. (1978) repeatedly administered CAT scans to eight alcoholics (mean age of 48,75 years, mean drinking history of 18,6 years). Repeat

scans, rated independently by two judges, revealed partial reversal of atrophy in four cases, all of whom remained abstinent between scans. Of those unimproved, two had continued drinking while the remaining two had ceased post-detoxification functional improvement before the intial CAT scan. It was found that cortical atrophy had reversed more than ventricular enlargement.

The authors concluded that the differences observed were too great and too sustained to be attributable solely to alcohol withdrawal syndrome resolution, the effects of which are biochemical, but should rather be attributable to structural changes. They cited animal research indicating inhibitory effects of alcohol on brain protein synthesis, which increases after cessation of alcohol consumption, and suggested a link between this and cerebral blood flow, reportedly reduced in alcoholics (Berglund & Ingvar, 1976).

Carlen et al. concluded that re-hydration of brain tissue could also not account for their findings, as this usually occurs shortly after withdrawal. Consequently, they proposed the argument that alcohol has toxic effects on brain neurons, killing some and incapacitating others through its action on supporting tissues. The cessation of alcohol comsumption is then seen as permitting regrowth of lost dendrites and re-arborization of incapacitated neurons, as well as restitution of supporting tissues.

In view of the limited degree of reversibility observed, Carlen et al. questioned the use of the word 'atrophy,' with its implication of irreversible death of cells, in alcoholic studies.

In a similar study, Carlen and Wilkinson (1980) divided re-scanned alcoholics into 'abstinent,' reduced drinking' and 'unchanged drinking' groups. No statistical differences on atrophy indices were found, though a statistical trend indicated increasing atrophy scores with greater amounts of alcohol consumed. The failure to attain significance here could be attributable to the small sample sizes used.

Ron et al. (1980) established cortical atrophy and ventricular enlargement in a large group of 100 alcoholics (43,5 years mean age; 17,3 years mean drinking history) relative to 41 control subjects (40 years mean age). On average the alcoholics were 34 days abstinent. When re-scanned a year later, abstinent alcoholics showed a decreased degree of ventricular enlargement, still greater than that of controls, although cortical indices were not reduced in all subjects.

Ron (1982) followed up on her original scans of 100 alcoholics, re-scanning 56 at intervals ranging between 30 and 152 weeks. At the time of follow-up scanning only 16 subjects were considered abstinent. No significant inter-scan differences were found on any indices used, although trends were observed in the abstinent sub-group towards both less severe cortical atrophy and ventricular enlargement.

Blind ratings of the pairs of scans for each subject allowed categorisation as either improved, unchanged or worse. These categories differed significantly as a function of days of abstinence before re-scanning ($p < ,001$)). Comparison of abstinent and drinking groups at re-scanning yielded no significant differences, although trends towards less severe atrophy were evident on two indices of cortical atrophy, in favour of the abstinent group.

It appears from these studies that a limited degree of reversibility of brain damage occurs in the alcoholic brain if abstinence is maintained. This reversibility is only partially due to resolution of the withdrawal syndrome and, possibly, it also reflects inproved cerebral blood flow and protein synthesis. The latter results in increased brain mass which, on the basis of animal data, might indicate the increasing formation of dendrites and arborisations.

The important finding is that the extent of reversibility is so small that it cannot, assessed by 'objective' means, attain statistical significance and even after a year of abstinence, leaves the alcoholic markedly deficient relative to controls. It can, thus, be concluded that

alcoholics suffer lasting degrees of brain damage which abstinence can no more than partially remedy and that relative to the normal population they will probably, for the rest of their lives, present a clinical picture of accelerated cortical and ventricular deterioration for their age.

1.3 THE FUNCTIONAL IMPLICATIONS OF PEG & CAT RESEARCH FINDINGS

The frontal lobes are regarded as the seat of 'associative' mental functions (McGhie, 1969). According to Lezak (1976) general problems associated with frontal lobe damage are mental slowing (apathy and decreased spontaniety), difficulties in making shifts of mental set (perseveration), deficient self-awareness and concreteness, with little sustained goal directed behaviour. Cognitive deficits are most associated with the upper and/or outer sides of the frontal lobes adjacent to the parietal and temporal lobes, both of which have also frequently been reported as atrophied in neuroradiological studies of alcoholics. More specifically, diffuse brain damage adversely affects memory, attention and concentration, impairs higher and more complex levels of thought and results in general response slowing. It is suspected that memory impairment might be a function of impaired concentration (Lezak, 1976).

Ventricular enlargement is the result of central atrophy, ie - the loss of subcortical cells, with resulting skrinkage of remaining white matter, reflected as widened ventricles. Both Lynch (1960) and Harper (1982) reported lesions in the tissues surrounding the ventricles. The thalamus and mammillary bodies were also implicated and it appears likely that other areas such as the hypothalamus and hippocampus might also be involved. It should be noted that the hypothalamus is believed to serve memory functions (Smythies, 1966). The thalamus regulates cortical arousal and is responsible for selective attention in conjunction with the frontal lobes (Maloney & Ward, 1976) and the hippocampus interconnects with both these bodies (Pribram, 1971). As it is argued that cerebral organisation is best described as "a complex of integrations

rather than specific and independant localisations of function" (Sarason & Sarason, 1980), it is likely that damage in any connected part of the brain might impair a function principally, though not exclusively, associated with another area. Thus the effects of diffuse cortical and central atrophy on attention, in particular, might arguably be great. Consequently, a wide range of functions for which the smallest amounts of attention are required may be impaired. Lezak (1976) goes further to claim that damage to the thalamus interferes with the integration of cortical centres which could impair all complex central processes.

1.4 PYSCHOLOGICAL DEFICITS ASSOCIATED WITH CHRONIC ALCOHOLISM

Reviewing the literature of the previous 25 years, Kleinknecht and Goldstein (1972) concluded that there was little agreement on which functions were most affected by prolonged alcohol abuse. The authors combined the deficits previously reported into two broad areas of abstract reasoning and problem solving and speed and complex psychomotor abilities. Within these two areas were subsumed deficits in abstract thought, numerical aptitude, manipulative problem solving, memory for spatial relations, discriminative ability, attention, psychomotor speed, finger and manual dexterity and motor co-ordination.

The authors notes, in addition, the observation made by Kish and Cheyne (1969) in one of the reviewed papers that the functional deficits exhibited by alcoholics in their thirties resembled those of normal subjects in their fifties. Kish and Cheyne proposed that the effects of alcohol abuse could be described as akin to premature ageing.

Lezak (1976) lists as typical of chronic alcoholics deficits in memory, cognitive set maintenance, persistence, visual search procedures, motor inhibition, organisation of perceptual-motor responses, synthesis of visual elements, temporal and spatial orientation and perseveration. These deficits are very specific, however, and in general they are referred to in terms of attentional disturbances, decreased conceptual

abilities, disorders of memory and meaningful use of language and intellectual deterioration (Anastasi, 1968). Learning difficulties have been noted, but are usually treated under the general heading of 'memory deficits.'

Usually, IQ scores do not reflect impairments in alcoholics (Ron, 1982), although it is frequently reported that performance tests in particular are subject to the effects of alcohol abuse. It would be expected that this would result in decreased full scale IQ, as well as a marked difference between verbal IQ and performance IQ, but this seldom occurs. However, when sub-tests are grouped the deficits are reduced, unless they occur on all sub-tests, as the remaining normal values raise the mean scores.

1.4.1 Recent Studies of Functional Impairment in Chronic Alcoholics

FitzHugh et al. (1960) compared a group of 17 detoxified chronic alcoholics to groups of brain-damaged and non-brain-damaged subjects matched on age, race, education and handedness. All subjects were hospitalised men, except one subject in the latter group.

Scores on the Wechsler-Bellevue Intelligence Scale for full scale IQ, verbal IQ and performance IQ (FSIQ, VIQ and PIQ respectively) indicated significant differences between the brain-damaged group and the other two groups, but no differences were found between the alcoholic and non-brain-damaged groups. However, on measures taken from the Halstead-Reitan Neuropsychological Battery, significant differences were found between alcoholics and non-brain-damaged subjects on the Impairement Index, Category Test and Tactual Performance Test scored for time. Only one sub-test statistically differentiated between alcoholics and brain-damaged subjects. The results, besides indicating significant deficits in abstract thought processes, concept formation and adaptive capabilities, cast doubt on the use of standard intelligence tests for diagnostic purposes in alcoholic populations.

In an attempted replication of the above study, FitzHugh et al. (1965) used groups of 35 male subjects, matched for age and education, representing the alcoholic, brain-damaged and normal populations. The groups were, on average, four years younger than in the previous study.

The same pattern of results emerged, with no differences observed between alcoholics and normal subjects on FSIQ, VIQ and PIQ, although normal subjects did prove significantly superior on Block Design. Alcoholics scored in the normal range for all Wechsler-Bellevue indices, on or above mean values, while the brain-damaged group consistently scored below mean values. On Halstead-Reitan tests, however, the alcoholics proved significantly inferior to normal subjects on seven of the ten subtests while, in turn, the alcoholics' performance was significantly superior to that of the brain-damaged subjects on seven sub-tests. Comparisons between normal subjects and brain-damaged subjects were significant in all cases.

Effectively the increased number of sub-tests differentiating alcoholics from normal subjects was a statistical phenomenon caused by the doubling of sample sizes in the replication. In the original study (1969) those tests which later achieved significance had all approached significance.

Dividing the samples at the age of 40 years into younger and older sub-groups, FitzHugh et al. further found that older subjects performed better on measures reflecting past experience and accumulated information while younger subjects were better at tests of adaptive abilities. Younger subjects in all groups were better on Wechsler Bellevue performance sub-tests and Halstead-Reitan sub-tests. In addition, comparison of Halstead-Reitan sub-test data trends within each diagnostic category indicated that differences between younger and older alcoholics were not as marked as in the normal group, and it was suggested that the data fitted an argument of premature ageing effects in the alcoholic group.

Talland (1963) investigated several types of reaction timing procedures

on currently abstinent alcoholics and control subjects matched for age and sex. The mean age of the alcoholic group was 42,2 years and all were in good health, none being colour-blind nor showing any signs of motor or neurological disorders. Results showed alcoholics slower on all forms of reaction time measurement. In his experiments Talland showed that alcoholics could not utilise alerting cues preceding stimulus onset as could controls, but that on the contrary, this slowed them down further. This, he argued, implicated central processes, not peripheral processes nor motor disorders.

Short and long term alcoholics were matched on age, education and drinking history by Jones (1971) and their performances compared on the Ravens Progressives Matrices and Shipley-Hartford tests, the former a predominently visual-spatial test of intelligence and the latter a test of verbal intelligence. This study was interesting in that duration of 'drinking' history was not taken as a possible independent variable, but was used as another matching variable, while the term of 'alcoholic' drinking was separately determined. The influence of the period of 'alcoholic' drinking, as distinct from the total length of drinking history on intellectual functions was assessed. Each pairing differed by at least five years on the 'alcoholic' drinking variable.

It was found, compared to an age and education matched hospitalised control group that alcoholics were significantly poorer in visual-spatial intelligence, but not in verbal intelligence. When the alcoholic sub-groups were compared, significant differences were found on both visual-spatial and verbal intelligence measures in favour of the short term alcoholic sub-group. Jones went on to correlate the two measures and found significant relationships between visual spatial and verbal intelligence in the control and short term alcoholic groups, but not in the long term alcoholic group. He concluded that with longer histories of 'alcoholic' drinking there arises a differential hemispheric sensitivity leading to dissociation of the intellectual functions involved. This, however, implies strict localisation of functions, which the majority of researchers reject because functions are subserved by association areas

quite remote from them.

However, the study has another merit, in that it offers a warning against the blind use of measures of verbal intelligence or vocabulary as approximations of premorbid intelligence, as these do not appear always to remain as impervious to alcohol abuse as was believed. It would be well to treat these findings only as suggestive, however, as samples were small and it appears likely that information on which the judgments of both duration of drinking history and durations of 'alcoholic' drinking were made might be inaccurate. This follows from reported consumption-minimising by alcoholics, which might extend beyond current drinking behaviour (Knox, 1980). In any event, the discernment of the point at which drinking becomes problematic must of its very nature be subjective and liable to large degrees of error.

Jones and Parsons (1971) compared groups of 40 abstinent alcoholics, hospitalised controls and brain-damaged subjects on the Category Test (part of the Halstead Reitan Battery), three sensory-motor tests and a measure of global intellectual functioning. Subjects were matched on age and education.

Major emphasis was given to the Category Test in an attempt to repeat the findings of FitzHugh et al. (1960, 1965), as the abstracting deficits reflected by high scores on this imply frontal lobe damage. Results indicated that the alcoholic and brain-damaged groups did not differ from each other, but both significantly differed from the control group. Significant differences were found between young and old subjects in the alcoholic and brain-damaged groups, but not in the control group, although in all cases the older subjects performed worse. Among younger subjects, controls and alcoholics did not differ significantly, but the brain-damaged group differed significantly from both. In older subjects, on the other hand, alcoholics did not differ significantly from brain-damaged subjects, but did differ significantly from controls. On the sensory motor tests, both group and age factors yielded significant results, but no differences were found between alcoholics and controls,

although the controls performed better. Younger alcoholics performed better than older alcoholics, as expected.

Finally, the alcoholic group was split into two groups matched for age and education, representing long and short term problem drinking histories, and it was found that the long term group made significantly more errors on the Category Test.

This study successfully replicated FitzHugh et al.'s (1960, 1965) results, and it was concluded that alcoholics probably suffer a mild form of brain-damage to the prefrontal area of the frontal lobes, or related sub-cortical structures, or both. It was also shown that with ageing, the rate of error production accelerates in alcoholics relative to other groups and that the error score varies as a function of duration of problem drinking. The alcoholic group also showed increased vulnerability with age in sensory-motor abilities, which was not the case in other groups.

The Wisconsin Card Sorting Test (WCST) reputedly is a test of abstracting ability and concept formation (Parker, 1980). Pendleton and Heaton (1982) compared it to the Category Test, finding the WCST more sensitive to frontal lesions, although the Category Test was more accurate diagnosing diffuse atrophy and a superior global index of brain damage, irrespective of nature or location. Tarter and Parsons (1971) compared alcoholic subjects to controls using WCST and found that alcoholics made more errors and took more trials to reach criterion. Contrary to expectations, the difficulty experienced by alcoholics was not due to perseveration, but to difficulty maintaining a pattern of search. It was argued on statistical grounds that frequent sequences of five correct responses before an error had a chance probability of $p < ,001$, and therefore proved the set had been acquired, yet could not be maintained to criterion. The alcoholics simply could not hold the set as well as controls.

This argues for lapses in concentration and distractability. Tarter and Parsons argued that this was consistent with sub-cortical damage, probably to the reticular formation. However, Maloney and Ward (1976) emphasised that selective attention is a joint function of both the thalamus and the cortex, so the conclusion can not be limited to central atrophy alone.

Tarter (1973) replicated the above study, dividing the alcoholic group once more in terms of duration of problem drinking. He found controls and short term alcoholics statistically indistinguishable, but long term alcoholics differed significantly on total trials, total errors and number of perseverative errors. He argued that the major cause of errors was a deficit in 'set persistence,' rather than a distinct perseverative tendency. Both alcoholic groups were deficient in this regard, the long term alcoholic group more so, although this group also had a greater tendency to repeat errors, ie - to perseverate. Tarter concluded that the results indicated frontal lobe atrophy.

Cutting (1978) found differences between alcoholics and controls on non-verbal memory and verbal fluency, but none on verbal concept formation and verbal learning. Heavy drinkers were significantly more impaired than light drinkers. Cutting suggested that non-verbal memory is a right temporal lobe function, not a frontal lobe function, drawing attention to the fact that the literature largely ignores the neuropathological and neuroradiological findings of diffuse symmetrical atrophy only preferentially, but not exclusively, involving the frontal lobes. However, it is still possible to account for non-verbal memory impairment in terms of frontal lobe atrophy impairing 'association' areas located there (McGhie, 1969). The fact that the function is markedly impaired does, however, argue more in favour of temporal lobe atrophy.

An attempt to derive a discriminant function capable of identifying alcoholics was made by O'leary et al. (1979) using orthopaedic patients and hospital staff as controls. All subjects were lower middle class males and groups did not differ on age and education. Persons with

diagnosed thought disorders, psychiatric symptomatology or history of drug abuse were excluded.

The alcoholics were tested on the Wechsler Bellevue and the Halstead Reitan battery between the 9th and 14th days of their inpatient programme, thus eliminating effects of alcohol withdrawal. The 20 sub-tests involved were statistically analysed for differences between groups.

The authors found that, contrary to expectations, of the 8 sub-tests which yielded significant differences, only two were Halstead Reitan scales. The Block Design sub-test was the best discriminator and it was found in developing a muliple regression prediction equation that none of the other scales could add significantly to that obtained from Block Design scores. This implies considerable overlap between the scales which yielded significant differences, Block Design being the best overall index of the combined deficient functions. O'Leary et al. concluded that their data indicated alcoholics to be deficient in abstract problem solving, visual-spatial co-ordination and perceptual-motor skills. These are all represented in Block Design performance. Overall, verbal tests on the Wechsler Bellevue did not discriminate as well as the performance tests.

Scores on the WAIS Block Design and Similarities sub-tests featured prominently in a discriminant function derived by Miller and Orr (1980) to differentiate between alcoholic and brain-damaged subjects. However, in another function differentiating between alcoholics and psychiatric controls (who of the three groups should most represent the normal population) WAIS sub-test scores were totally unrepresented, only Halstead Reitan scores contributing meaningfully. In the former case, the logical deduction is that abstracting ability and capacity for conceptual thought, the common features between performances on the Block Design and Similarities sub-tests, distinguish between alcoholics and brain-damaged subjects. In the latter case, the difference between this equation and that derived by O'Leary et al. (1979) in terms of the number of variables involved and the nature of such variables,

conceivably derives from the differing groups from which subjects representing the normal population were drawn: hospital staff and orthopaedic patients in O'Leary et al.'s study, and psychiatric patients in this one. These differences might involve abstract problem solving and the integrative central component of perceptual-motor performance.

The authors did, however, find significant deficits in alcoholics on WAIS performance sub-tests, relative to psychiatric subjects. In addition, they interpreted their data as consistent with advancing global impairment, as distinct from a developmental sequence, associated with length of drinking history, in alcoholics. Their data thus supported the 'premature ageing' hypothesis cited previously.

Ryan (1980) studied memory and learning in alcoholic and control subjects. Using a variety of methodologies Ryan finally concluded that it could not be proved that alcoholics suffered durable memory and learning deficits, but problem-solving remained deficient for at least several months after detoxification.

Controls were superior in delayed recall, alcoholic subjects not even being able to use mnemonic techniques spontaneously. When instructed to use such techniques, however, the difference was greatly reduced, alcoholics performance alone responding. Similarly, the use of prompts in certain tasks showed that 'forgetting' was largely the result of poor retrieval operations, not defective encoding or storage, on the part of alcoholics. Ryan suggested that memory be regarded as a creative skill heavily dependent on problem solving abilities, poor memory being principally the result of deficient problem solving skills.

A large scale study by Ron (1980) used 100 alcoholic subjects and 50 controls. On average the alcoholics had been abstinent for 34 days and all subjects were screened for possible brain damage of non-alcoholic origin. When age and premorbid IQ were controlled it was found that alcoholic subjects were significantly cognitively impaired compared

to controls. Dividing the groups into high and low IQ sub-groups it was found that differences were accentuated between the higher IQ sub-groups. Ron proposed a 'floor effect' active in low IQ alcoholics, arguing that these subjects have a smaller 'alcohol-vulnerable' component of cognitive abilities and, hence, could not show as large a set of impairments relative to IQ matched controls. Memory impairments persisted beyond acute withdrawal, this suggesting either very long recovery periods or irreversible damage. Ron supported Tarter and Parson (1971) and Tarter (1973) in their findings of alcoholics making frequent perseverative errors and experiencing difficulty in maintaining a cognitive set.

Specifically, alcoholics and controls differed on an overall measure of verbal IQ, verbal and performance WAIS sub-tests, aspects of immediate and delayed recall, and cognitive set maintenance. Considering the higher premorbid IQ subjects alone, all comparisons except for the verbal IQ test became significant. In considering lower premorbid IQ subjects, only tests of delayed and immediate recall of logical memory showed significant differences.

1.4.2 Reversibility of Functional Deficits after Alcohol Withdrawal

Psychometric assessment of alcoholics in acute withdrawal is almost certainly invalid as an indication of their normal levels of functioning (Lezak, 1976). In this phase both physical and psychological equilibrium are disturbed and, consequently, poorer scores can be expected.

Individuals appear to vary greatly in their reactions to alcohol withdrawal, some experiencing delirium tremens and alcoholic hallucinosis, while others appear to escape unscathed. Although the argument from CAT studies that reversibility of atrophy must reflect morphological rather than biochemical changes appears sound, it is not clear at what point biochemical parameters re-stablise. Several studies have investigated logitudinally the effects of withdrawal and abstinence over varying periods and these offer some clues as to the point after which deficits might be regarded as stable.

Page and Linden (1974) tested five groups of alcoholics after detoxification on the WAIS, Trail Making Test and Benton Visual Retention Test. One group was tested one week after withdrawal and others after two, four, six and eight weeks respectively. This design was used to counteract learning effects.

Most improvement was found between scores at week one and week two, the graph of improvement thereafter becoming almost asymptotic, but with clear deficits relative to standard norms still evident after eight weeks. Functions observed to improve between weeks one and two included abstract reasoning, visual motor co-ordination, spatial ability and short term memory. However, Page and Linden only tentatively accepted these improvements, arguing that assessments at week one might in fact have been abnormally depressed by lingering effects of withdrawal, and that the resultant functional improvement might be spurious. The authors cautioned against assessment too soon after detoxification. Their findings received support from a similar longitudinal study by Page and Schaub (1977) where post-withdrawal improvements did not continue beyond week three, although still abstinent alcoholics were re-assessed after six months.

However, improvement was observed over a one year period of abstinence by Long and McLachlan (1974) who re-tested a group of seventeen alcoholics. Many scales of the Halstead Reitan battery showed gains, including the Category Test. Significant improvements were found in WAIS performance, but not verbal sub-tests. The authors concluded that with abstinence there are improvements in cognitive, perceptual and motor abilities, but that some abilities were still impaired after a year and possibly needed longer periods to recover, if they were not permanently impaired.

However, if one considers the likely contribution of learning effects being responsible for a large portion of the observed gains, the claims of this study might be reduced. Certainly, performance tests are known to be highly susceptible to practice effects.

Limited evidence of the differential effects of abstinence and continued alcohol consumption was obtained by McLachlan and Levinson (1974), who re-tested large groups of abstinent and drinking alcoholics after one year, using the Block Design sub-test of the WAIS. Analysis showed that abstinent alcoholics scored significantly higher at the re-test than drinking alcoholics, and that the abstinent group improved significantly over the intervening year, while drinking alcoholics did not.

Clarke and Haughton (1975) assessed heavy drinkers two, six and ten weeks after withdrawal on the WAIS Similarities, Vocabulary, Block Design and Object Assembly sub-tests, as well as a visual reproduction test. A control group was tested twice, with a four week interval. Heavy drinkers performed worse on all measures except Vocabulary, at all assessments.

Most improvement occurred between the first and second assessments, but the trend continued to the third assessment. This was taken as indicating that functional recovery is still continuing after ten weeks of abstinence. Grant et al. (1979) compared a recently detoxified three week abstinent alcoholic group to an eighteen month abstinent alcoholic group, using the WAIS and the Halstead Reitan battery. The authors found no differences between the groups according to the proportions of each rated as impaired, and concluded that alcoholics after three weeks abstinence can become 'essentially normal neuropsychologically.'

However, a one year follow-up study related to that of Grant et al. (Adams, et al., 1980) recorded different gains in the three groups, with more significant gains achieved by the control group. The longer abstinent group recorded fewer significant gains than the control group, but far more than recorded in the less abstinent group. The authors proposed that at the time of the previous study a sub-clinical form of deficit, impairing incidental learning, went unnoticed and this gave rise to the failure by this group to record practice effects. However, the data on subject abstinence during the intervening period are very

sketchy and it might well be that the poorer performance of the 'less abstinent' group reflects undisclosed drinking behaviour which differentiates this group from the others. A further criticism of the original study (Grant et al., 1979) is that it was subject to selection bias in that only available, ready-formed groups were assessed. It has been shown (Clarke & Haughton, 1975) that subjects who drop out of longitudinal studies tend to have had poorer scores at initial assessment. This tendency thus enhances the mean score of the group at later assessments, leading to more 'normal' scores.

Guthrie and Elliot (1980) reported a significant reduction in the number of psychometric indices on which their alcoholic group exhibited deficiency after six months, if they remained abstinent. Performance of those subjects who continued drinking between assessments was even more impaired at re-assessment.

A study by Schau et al. (1980) found alcoholics functionally impaired at both initial testing and at re-testing, on average, 14 months later, relative to a control group. Initial testing was conducted 9 to 14 days after alcohol withdrawal. Particular improvements were observed on WAIS performance sub-tests. A factor of relevance to other studies was the estimation of the strength of practice effects, which were shown to be very weak in alcoholics.

Eckhardt et al. (1980) assessed two groups of alcoholics, abstinent for either 2 to 6 days, or 14 to 31 days, on a battery of 24 tests, including WAIS sub-tests, the Halstead Reitan battery and the Wisconsin Card Sorting Test. The subjects were all males in their mid-thirties and the groups were matched for age and education. The less abstinent group was rated impaired on 13 of the 24 tests, while the more abstinent group was rated impaired on 11 of the same 13 tests, but on none of the others. For the latter group impairments were mostly found on Halstead Reitan indices. Scores tended to be marginally superior in the more abstinent group, but statistical analysis failed to reveal any overall differences between the groups, using age and education as co-variates.

The above studies conflict in their conclusions. Page and Linden (1974), Page and Schaub (1977) and Grant et al. (1979) recorded no improvements beyond the third week of abstinence. The rest of the studies recorded continuing improvements up to as much as thirty months. It is, however, arguable that in the event of practice effects being controlled in certain of the latter group of studies, the conclusions drawn might have been different. However, the size of control groups in certain of these studies (eg - Clarke & Haughton, 1975; Schau et al., 1980) strongly indicates that practice effects cannot fully account for observed gains, and that functional recovery continues considerably beyond three weeks, though at a much slower rate. Consequently, caution must be exercised in interpreting tests scores obtained shortly after the resolution of the alcohol withdrawal syndrome, as these scores may seriously underestimate the future functional capabilities of those assessed. In this regard it is of relevance that Lezak (1976) advises that for any form of assessment of brain damage, testing should take place between three and six months after the trauma, to ensure validity of the test results.

1.5 A SUMMARY OF IMPAIRMENTS IN CHRONIC ALCOHOLICS REPORTED IN NEUROPATHOLOGICAL, NEURORADIOLOGICAL & NEUROPSYCHOLOGICAL STUDIES

The findings of neuropathological studies on alcoholic brains, two of which used normal controls, are unanimous in finding greater degrees of diffuse cerebral atrophy in the brains of chronic alcoholics. Two of these studies (Courville, 1955; Lynch, 1960) specifically indicate preferential involvement of the frontal lobes, and in the two studies mention is made of co-existent sub-cortical atrophy, but in all studies the primary emphasis is laid on advanced cerebral (cortical) atrophy in alcoholic brains. Lynch (1960) estimated cell loss in alcoholics, relative to matched controls, at between 20% and 40% and Harper found brain weights of alcoholics considerably less than those of non-alcoholics.

Studies utilising pneumeoncephalograms and computerised axial tomography are more abundant than neuropathological studies, but great uniformity

is evident in their conclusions. Repeatedly results show very large proportions of the alcoholic samples studied suffer mild to moderate cerebral atrophy while some, more rarely, also record more limited incidence of severe cerebral atrophy. Ron (1982), however, found that in only a small minority of alcoholic cases were the degrees of cortical atrophy and ventricular enlargement comparable to those found in dementia cases and most findings are in agreement with her claim.

In all cases cerebral atrophy is reported as diffuse and symmetrical, many studies emphasising greater damage to the frontal lobes, while the temporal and parietal lobes suffer less involvement. A small incidence of cerebellar atrophy is also frequently found.

Sub-cortial atrophy, in the form of ventricular enlargement, is frequently reported, but in general fewer subjects suffer this than cerebral atrophy. When ventricular enlargement does occur this is usually in conjunction with cortical atrophy, rather than in isolation. Although several of the above studies did not include control groups and thus involve some subjectivity in ratings of presence and degrees of atrophy, many other studies do include non-alcoholic control groups and no great differences are discernable between the findings of these studies.

Studies which evaluate the effects of abstinence report a limited degree of recovery of brain mass. No statistically significant differences were found by either Carlen and Wilkinson (1980) or Ron (1982), though both reported statistical trends indicative of increasing brain mass with abstinence. It appears likely that these statistical trends, if not entirely spurious, would only attain statistical significance if very large samples were to be used. This appears to imply that even over the long period of Ron's (1982) study, recovery due to abstinence in extremely limited in extent and that alcoholics have little chance of fully regaining 'normal' brain mass.

Psychometric studies have used a wide variety of test materials, many of which are not directly comparable. It frequently emerges that on

standard measures of intellectual capacities, alcoholics score well within the normal ranges and are indistinguishable from the general population (FitzHugh et al., 1960; 1965). As the evidence from neuropathological and neuroradiological studies indicates that alcoholics are a brain-damaged population, this might be regarded as unexpected as on standard IQ tests identified brain-damaged groups are easily identifiable by a marked deficit in performance IQ relative to their obtained verbal IQ scores.

However, numerous studies have shown that tests particularly sensitive to the organic state of the brain, especially the Halstead Reitan and Luria Nebraska neuropsychological batteries, do discriminate between alcoholics and non-alcoholics. It has been argued that the limited deficits observed on standard tests of intellectucal ability are ascribable to their measuring crystallised intelligence, which is relatively impervious to the toxic effects of alcohol, while 'biological' or adaptive intelligence is detrimentally affected (Chelune, 1982).

Repeated findings of deficits in alcoholics on the Halstead Reitan Category Test, the Wisconsin Card Sorting Test and the WAIS Block Design Test indicate impairments in the non-verbal concept formation, abstract thought and complex psychomotor ability in alcoholics. Particular attention has been directed at the failure of alcoholics to persist with a set, which appears to indicate a high degree of distractability. General performance on neuropsychological batteries indicates poorer adaptive capacities with respect to novel problems, compared to that of the non-alcoholic population.

In addition, memory deficits are frequently reported and, less frequently, deficits in visual-spatial abilities. Although scores on WAIS and Wechsler Bellevue scales tend to remain within normal limits, scores on most scales are found to reflect slight non-significant deficits compared to normal subjects.

Attempts have been made to relate psychological deficits in alcoholics

to drinking related variables. No consistent results have emerged and the most regularly related variable is age. There are growing indications that with increasing age, irrespective of the total amount of alcohol consumed in the past, the brain becomes increasingly vulnerable to the toxic effects of alcohol.

Indications are that with abstinence, psychological performance of alcoholics improves slightly, but this appears to be a protracted process and total recovery appears unlikely. Overall, the three sets of studies cited above reflect morphological and functional abnormalities in alcoholics. With abstinence a limited degree of recovery of brain mass and of functional capacities appears possible, but in both instances alcoholics are left with long term deficits which are unlikely to be totally eliminated.

Although the evidence of deficits both morphological and functional is disputable, the relationship between the two is not clear. Carlsson et al. (1979) related many indices of cortical atrophy and ventricular enlargement to psychometric performance. Though several significant correlations were found, the highest of these yielded a co-efficient of 0,46 which is of little practical significance. Wilkinson and Carlen (1980) found small significant correlations of most WAIS sub-tests to sulcal enlargement, a measure of cerebral cortical atrophy, while Zelozowiki et al. (1981) found numerous correlations of psychometric indices to ventricular enlargement, though none exceeded a value of 0,50. Graff-Radford et al. (1982) found modest, but significant, correlations of both cortical and sub-cortical indices of atrophy to psychometric performance. On the other hand, both Lee et al. (1982) and Ron (1982) found no correlations between these sets of measures.

The above findings are inconsistent in that relationships are found only in some cases, despite large sample sizes, which tend to yield significant results. Some findings indicate cerebral atrophy relates to psychometric performance, while others indicate that ventricular enlargement correlates with psychometric performance. In a minority of cases

some indices of both cerebral and central atrophy have been correlated to psychometric performance.

The one common feature among these findings is that where a significant correlation co-efficient is obtained, its value is modest, and any regression equations utilising these co-efficients are consequently of little practical significance as predictions based on these are subject to large degrees of error. Thus it is very dangerous to attempt to interpret scores from either set of indices in terms of the other.

However, despite the obscure relationship between the morphological and functional aspects of impairment in alcoholics due to the toxic effects of alcohol, the evidence of the existence of long term impairments on both types of assessment is overwhelming.

2. PIRACETAM

2.1 THE PHARMACOLOGICAL ACTION OF PIRACETAM

Piracetam is a cyclic derivative of gamma-amino-butyric acid (GABA), an important mediator in brain cell bio-energetic processes. As GABA does not cross the blood-brain barrier, its levels cannot be manipulated directly. Piracetam has been shown to cross the blood-brain barrier (Calliauw & Marchau, 1975), however, and appears to take on some of the functions of GABA while not influencing GABA levels in the brain. The total mechanism of action of piracetam is complex and as yet imperfectly understood.

The main effect of piracetam is in increasing the turnover of adenosine triphosphate (ATP), a substance known for its role in the storage of energy in brain cells. This energy is used, resulting in increased synthesis of macromolecules, including ribonucleic acid (RNA). In so doing, overall cell metabolism is increased and this, in conjunction with an enhancing effect on blood erythrocyte deformability, leads to a gross improvement in microcirculation in cases where microcirculation is inadequate (Garay & Costa, 1979; Herrschaft, 1979; Nalbandian, 1979).

Animal studies have revealed that piracetam has no sedative, tranquillising or stimulatory effects, nor does it affect the cardiovascular, respiratory or gastro-intestinal functions (Guirgea, 1973). Piracetam does not accumulate, although a small amount of renal reabsorbtion has been recorded and it is excreted unmetabolised (Gobert & Baltes, 1977). It has no known side effects, nor has it been known to interact with other medications.

In humans piracetam can be detected in all organs, but has its longest half-life in the brain, this being approximately 7 hours and 40 minutes, compared with a blood half-life of about 5 hours and 18 minutes (Calliau & Marchau, 1975). Peak blood levels in man are attained about

forty minutes after administration and in fasting humans excretion is almost complete after thirty hours.

2.2 THE EFFECTS OF PIRACETAM IN ANIMAL STUDIES

Guirgea (1973) reviewed much of the literature concerning the effects of piracetam on animals. Piracetam was shown to protect the brain from experimentally induced hypoxia, to facilitate learning and memory functions, and to offset treatments designed to interfere with learning and memory. Piracetam reduced the loss of acquired learning substantially, but more so when administered prior to learning, rather than after amnesic treatment (electroconvulsive shock).

Because of the beneficial effects demonstrated, Guirgea argued that piracetam must be active in the central nervous system. Citing EEG evidence which indicated influence restricted to cortical associative areas, Guirgea concluded that piracetam acts at the telencephalic level of the forebrain and has no direct effects on the limbic or reticular formations, the thalamus or peripheral functions.

Burnotte et al. (1973) studied the effects of piracetam in ageing rats, in whom the process involving RNA synthesis was in decline. The authors found evidence of enhanced brain cell efficiency and increased presence of substances critical to protein synthesis than in untreated animals. Consequently it was concluded that piracetam improves the processes of protein synthesis and, as long term memory depends on protein synthesis in brain cells, that this held possible implications for memory and learning functions. Bonifaci et al. (1982) obtained similar findings. Additional support for the argument for facilitation of brain RNA and protein synthesis was obtained from a study on spinal fixation time (UCB, 1980). Piracetam was shown to shorten the time taken to encode learning at the spinal level. This action is common to drugs which enhance RNA and protein production in the brain.

In further studies reported (UCB, 1980) piracetam was found to inhibit

central nystagmus provoked in rabbits by electrical stimulation of the lateral geniculate body. As it is possible to facilitate nystagmus by inducing cortical spreading depression through the application of potassium chloride to the cortex, it was argued that the cortex exercises a form of control which limits the extent of nystagmus under normal conditions. The improved inhibition observed under the influence of piracetam argued, since its action was known from previous studies to be solely cortical, for enhanced cortical control of sub-cortical brain structures (Guirgea & Salama, 1977).

Combined with the findings from other studies which indicate improved interhemispheric communication via the corpus callosum (UCB, 1980), it appears from animal studies that the action of piracetam at the level of the cell is one of increased turnover of cerebral energy, resulting in improved metabolism and increased functional capacity, and protection against toxic, anoxic and hypoxic effects, while at a functional level this appears as overall enhancement of learning, resistance to impairing agents, improved integration of the cerebral hemispheres and increased control exercised by the cortex on sub-cortical functions (Guirgea & Salama, 1977). The above features suggest that piracetam could be usefully applied to human subjects.

2.3 PIRACETAM IN HUMAN CLINICAL TRIALS

2.3.1 Studies outside the Area of Chronic Alcoholism

Lagergren and Levander (1974) examined the action of piracetam on perceptual and psychomotor functions under conditions of experimentally induced hypoxia, using twelve subjects equipped with artifical pace-makers. The authors found that while on placebo, subjects were severely functionally impaired by a reduction of heart rate from a normal value of 70 beats per minute to one of 45 beats per minute, although subjects were not able to detect the differences in heart rate. Under piracetam these impairments were all reduced, though not all reductions were statistically significant. The authors concluded that their findings were consistent with either a protective effect or a cortical arousing effect, counter-

acting the expected decrement in vigilance associated with induced hypoxia.

In a similar study, also involving subjects fitted with pacemakers, Isaksson et al. (1975) found, within a double-blind methodology involving piracetam and a placebo, that the effects of piracetam were evident on the EEG even at normal heart rates. The authors had expected that the effects of piracetam would only become evident in the induced hypoxia condition.

The effects observed in this study were small and were not detectable by visual inspection, but were detected by on-line computer analysis. The differences were, however, statistically significant, reflecting a decrease in slow EEG activity due to piracetam. The authors concluded that the effect of piracetam was not limited to protection against hypoxia and that the alternative possibility mentioned by Lagergren and Levander (1974), namely, that piracetam had a cortical arousing effect, received support from these findings.

Dimond (1975) investigated the effects of piracetam on verbal learning in 16 student subjects, using a placebo controlled double-blind procedure. No differences were apparent after one week of treatment, but significant improvements in favour of piracetam were found after two weeks. Trends indicating improved delayed recall in the piracetam group were also reported.

Dimond (1975) also assessed these subjects' performance on a dichotic listening task and reported an improvement of approximately 15% under piracetam treatment, but this result did not achieve statistical significance. Further examination, however, revealed that most of the improvement was due to improved recall of items fed to the left ear which meant that, for recall to occur, this information had to be transferred from the right cerebral hemisphere to the left, via the corpus callosum. The improved recall of these items when piracetam was given was consistent with the findings of animal studies reported by

Guirgea (1973) which reflected improved interhemispheric transfer of information.

Using a double-blind design, Wedl and Suchenwirth (1977) compared the effects of piracetam and placebo on a group of 24 students. Over a five day period, the authors found positive effects due to piracetam on mental tone, alertness and learning.

*Dema*y and Bande (1980) used a low pressure tank to examine the effects of piracetam and placebo on visual attention and concentration under conditions of induced hypoxia. The subjects were 12 normal volunteers and a double-blind procedure was employed. It was found that under hypoxic conditions speed of test completion was not differentially affected by piracetam compared to placebo, but the proportion of errors decreased with piracetam. The effects of piracetam were more marked in the longer periods of hypoxia and the authors concluded that piracetam protected mental efficiency under hypoxic conditions.

The above findings were all derived from cerebrally normal subjects and reflect the findings of animal studies. It should be noted that both Dimond (1975) and Lagergren and Levander (1974) found that subjects could not distinguish between piracetam and placebo treatments, thus ruling out the possibility of contamination of results through perceived demand effects.

The effects of piracetam were also evaluated in several non-alcoholic clinical populations. Patients undergoing surgery involving general anaesthesia were studied to extend the animal findings that piracetam protects the brain against the effects of hypoxia. Richardson and Bereen (1977), Rivas Vidal (1979) and Samayoa de Leon (1979) all reported beneficial effects attributed to piracetam, in terms of raised post-operative levels of consciousness, shortened recovery times and faster elimination of the toxic effects of anaesthesia. Dosages in these studies were large and appear to indicate that piracetam has no detectable toxic effects in dosages up to 10 grams per day (Richardson &

Bereen, 1977). Beneficial effects on post-operative levels of consciousness, but not on survival rates, were also reported in a study of head injury patients (Calliau & Marchau, 1975). Schvartsman (1979) found that piracetam shortened periods of coma resulting from overdoses of psychotropic drugs.

Volavka et al. (1979) found that piracetam increased overall EEG frequencies in a group of children with learning disorders. As these children usually exhibit EEG slowing, the authors contended that piracetam appeared to remediate this problem, and probably increased alertness and decreased fatiguability. Interestingly, the authors described the piracetam-induced EEG changes as similar to those obtained after administration of amphetamines. As amphetamines are psychostimulants, this isolated finding appears to run counter to earlier reports (Calliau & Marchau, 1975) that piracetam has no stimulant properties.

Similar findings to those of Volavka et al. (1979) were obtained by Bente (1977) in a study of eleven elderly subjects. Bente observed reduced slow frequencies in the delta and theta bands, a slight increase in beta frequencies and a marked increase in alpha frequencies under piracetam treatment and concluded that these changes reflected improvements upon previous levels of vigilance regulatory functions.

Mindus et al. (1977) examined the effects of piracetam on perceptual motor ability in an ageing but unimpaired sample. The authors found, using a double-blind placebo controlled design, that piracetam proved superior to placebo on most tests. Self-ratings of improvement, while indicative of improvement, did not attain significance, however, possibly indicating that the changes were too small or too subtle for the subjects to detect. The authors concluded that piracetam enhanced mental alertness and cortical functions.

Ageing persons frequently suffer disturbances of the cerebral blood supply, resulting in ischemic (undersupplied) areas and hyperemic

(oversupplied) areas. It has been found that manipulation of venous blood supply does not remedy these imbalances. However, Heinitz (1975), using a brain scintigram technique, found that piracetam acted to restore balanced cerebral blood flow, but the improvement disappeared after the withdrawal of piracetam treatment.

Heinitz found the improved cerebral blood flow related to positive changes in alertness, attentiveness, memory and speech. He argued that age-related decreased GABA production resulted in dysfunction of inhibitory neurons due to energy shortages in these neurons, and that the result of this was increased overall excitability of the central nervous system. Heinitz claimed this excessive excitability expressed itself as great distractability, which could be diminished by piracetam. Herrschaft (1979) recorded similar findings on regional cerebral blood flow, adding that piracetam showed its activity in the grey matter only, that is, only in the cortex.

The dominant emphasis in piracetam studies appears to have fallen on piracetam's efficiency in the treatment of the psycho-organic syndromes of ageing (Suchenwirth, 1979). Reviewing the literature of German studies on piracetam in these syndromes, Suchenwirth concluded that the most frequently reported improvements were in vigilance, lucidity, drive, mood, concentration, memory, orientation and aphasia. Caro Mendevil (1979) also cited findings of improved psychmotor functions, but both he and Chouinard et al.(1979) gave prominence to findings of improved alertness or awareness while, in general, they and Castellanos et al. (1979) supported Suchenwirth's conclusions. However, Skondia (1982), in a study using more objective measures, found improvements on the WAIS Object Assembly and Similarities sub-tests, but not on the Block Design, Digit Symbol, Digit Span or Information sub-tests. The failure to record significant improvements on the Block Design and Digit Symbol sub-tests, in particular, was unexpected, as these tests have frequently been reported as most sensitive to any form of brain impairment. Skondia's findings are, therefore, somewhat equivocal. Piracetam has also been found useful in the treatment of depression (Kabes et al., 1979).

2.3.2 Piracetam Research in Alcoholism

2.3.2.1 Acute Withdrawal Syndrome:

Several studies have evaluated pireacetam's efficacy in the treatment of various aspects of alcoholism. Studies of the acute withdrawal syndrome relate in nature to studies of the efficacy of piracetam in post-anaesthetic recovery and treatment of overdosage cases involving psychotropic drugs.

Knott and Beard (unpublished paper) conducted a placebo-controlled randomised double-blind trial utilising both rating scales and standardised tests. Results indicated no differences on perceptual motor tests, but significant differences in assessment of symptom severity after 2 and 3 days. In particular, beneficial effects on vigour and fatigue items and items related to confusional states were noted in piracetam treated subjects. These results were replicated by Petty (unpublished paper), except that he did not attempt assessment of perceptual motor functions. Ulbricht (1976) concluded that piracetam was a useful adjunct to standard treatment of withdrawal syndrome, finding that it controlled states of delirium and pre-delirium in all cases except those involving alcoholic epilepsy.

Marks (1977) presented findings that piracetam did not generally differ from chlorpromazine, another medication used in the treatment of withdrawal states, both showing beneficial effects. However, the results showed piracetam caused less ataxia and drowsiness and more social interest. Findings of less lethargy and more sociable behaviour were also reported by Almeida Vargas (1979).

2.3.2.2 Chronic Alcoholism:

Binder (1974) conducted a placebo controlled blind clinical trial involving 50 male alcoholic inpatients who were regarded as having completed withdrawal and who were not taking psychtropic

medications. The groups were matched for age, education and duration of alcoholism. A battery of psychomotor tests and self-rating scales was applied at the commencement of the study and after six weeks. Binder recorded improvements over the period of the trial in both groups, but the piracetam treated group showed superior improvement. Results indicated that piracetam did not enhance performance on 'stimulus response' type tasks, but influenced the extent, speed and quality of constructive performance. Binder concluded that piracetam improved concentration and co-ordination of higher mental functions, reflecting enhanced functional potential of the cortex. Subjectively, subjects rated themselves as more inclined to work, and more peaceful.

A placebo controlled double-blind crossover design was used by Binder and Doddabela (1976) to study the effects of piracetam on 40 detoxified alcoholic subjects over a period of 14 to 18 weeks. Subjects were assessed on a battery of psychometric tests and the authors found improvements in associative and discriminative aspects of learning and in concentration. Further analysis of their data led the authors to conclude that the observed significant results reflected general, non- specific enhancement of functions due to treatment with piracetam. They considered this a result of "more regular, stronger and continuous cortical activiation."

3. THE AIM OF THIS STUDY

Neuropathological and neuroradiological studies cited above have repeatedly shown alcoholic subjects to exhibit advanced cortical atrophy and ventricular enlargement for their ages. This has been shown to revert partially towards normal values when abstinence from alcohol is maintained, but the available evidence indicates that total recovery is unlikely or, at least, extremely protracted. Similarly, neuropsychological studies have regularly indicated functional impairments in alcoholic populations, which only partially recede with abstinence.

The precise nature of the link between morphological and functional abnormalities in this population is not clear. However, correlations between morphological and functional impairment indices, while not large and while not being of great predictive value, nevertheless frequently attain statistical significance. It thus appears likely that in some as yet unclear fashion, morphological abnormalities do underly the function deficits recorded in the alcoholic population.

Clearly, the collective contributions of cortical atrophy and sub-cortical (central) atrophy, as reflected by ventricular enlargements towards these observed functional deficits, are not yet known. However, the literature has shown that cortical atrophy is found more frequently than central atrophy, and certain studies have recorded central atrophy predominently or exclusively in the presence of cortical atrophy. Central atrophy is only reported consistently in older alcoholic populations and appears to makes its appearance at a later stage than cortical atrophy. Both forms of atrophy advance with ageing, but the advance is accelerated by alcohol abuse.

Consequently, it appears that the functional deficits exhibited by young alcoholics are more likely to reflect cortical atrophy that central atrophy. There is no reason to expect that cortical atrophy should not

continue, with advancing age, to contribute to functional impairments, although later central atrophy might well lead to additional impairments or to strengthening of impairing mechanisms.

There is, then, reason to expect that a drug which is claimed to enhance the level of functioning of cortical neurons and cells might partially remedy the functional deficits associated with cortical atrophy. In the brain the action of piracetam is predominently in the grey cortical matter. Piracetam increases the production and turnover of adenosine triphosphate(ATP), a substance which stores energy for use in brain cells. As all membrane phenomena and nervous conduction, as well as the synthesis of nucleic acids and proteins depend on a regular supply of ATP, piracetam optimises cellular and neuronal functions. This has been shown to have protective aspects, where stored ATP may enable cells to survive acute intoxications and hypoxia and a 'cortical arousal' effect which goes beyond mere protective functions.

As aspects of attention and concentration fall under the joint action of both cortical and sub-cortical areas of the cerebrum, it is possible that vigilence, attention and concentration might be improved by purely cortical treatment. The findings of numerous studies support the view that piracetam does not directly affect specific functions, but that the improvements noted reflect improved concentration, alertness, arousal, vigilance and attention.

Consequently, it appears that piracetam might be useful in the treatment of long term psychological deficits which result from alcoholism through a general raising of the level of arousal. While improvements might occur across the entire spectrum of psychological functions, whether intact or deficient, attention should centre on the deficient functions as elimination of these problem areas is of greater clinical importance than the enhancement of normal functions.

Two studies cited above have evaluated the utility of piracetam in chronic alcoholism. Both reported promising findings, but the issue is

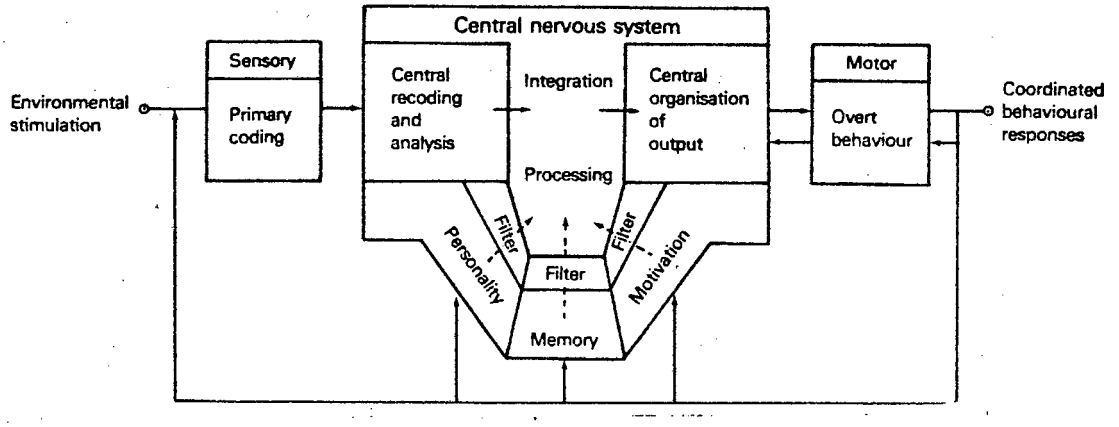
far from settled, as both studies used limited batteries of tests and one study (Binder, 1974) was only a single-blind clinical trial, and this might have been susceptible to contamination. Further, both studies could be contaminated by testing being conducted too soon after detoxification, as this would probably yield spuriously low baseline scores. Subsequent improvements in levels of functioning would then erroneously be attributed to the treatments applied. In addition, the findings of Binder and Doddabela (1976) are not wholly convincing, as no differences between treatments were detected on a substantial number of methods used.

The common claim of both Binder (1974) and Binder and Doddabela (1976) that piracetam improves co-ordination and co-operation of psychological functions is, however, in line with both the findings of improved interhemispheric communication (Guirgea, 1973; Dimond, 1975) and those of improved cortical control of sub-cortical structures (Guirgea & Salama, 1977), reported earlier.

Seen in terms of the model created by Hindmarch (1980) presented in Figure 1, this action of piracetam would be on the central integrative and processing functions which are modulated by, inter alia, the level of arousal of the central nervous system. Although the model is expressly designed to account for psychomotor functions, it is capable of accounting for a wide range of test performances and it seems as though it can be extended to more verbal and abstract functions without difficulty in the case of piracetam as its action, being central in nature, can be pertinent to any test performance.

Due to the lack of clear cut findings in the study of piracetam's effect on functional deficits resulting from chronic alcoholism, studies in this area should be regarded as exploratory. The claims of an overall 'arousing' effect appear to justify application of a wide range of measures in any such study, but these should be selected either on grounds of demonstrated deficient performance by alcoholics on these measures, or because the measures have been shown sensitive to brain

FIGURE 1: Hindmarch's Model of Psychomotor Function.



Psychomotor performance results from the co-ordination of sensory and motor systems through the integrative and organisational processes of the brain and central nervous system. The processing of sensory information is influenced by personality, memory and individual motivation, while the overall function of the integrative mechanism is governed by the state of arousal of the central nervous system. Complex feedback and adaptive systems complete the process by which environmental stimuli produce appropriate, co-ordinated behavioural responses.

---

damage in other populations.

As psychometric performance might be influenced by acute intoxication effects, acute withdrawal effects or long term functional deficits of alcoholism, singly or in varying combinations, the former two sets of variables should be eliminated in order to study the latter without contamination.

Consequently, the effects if piracetam should be evaluated on a wide range of measures of psychological functions in a sample of chronic

alcoholics currently free of problem drinking and which has been so for at least three months. A placebo controlled randomised double-blind crossover design comprising two eight week periods should provide maximal internal validity.

3.1 EXPERIMENTAL HYPOTHESIS

The adminstration of piracetam and placebo for two 8-week periods to the two treatment groups will result in systematic differences between groups in test scores obtained after each 8-week period, that is, differences are expected at assessments after 8 weeks and after 16 weeks, but not at baseline, and the direction of the differences should relate systematically to the relative effectiveness of placebo and piracetam in influencing functional performance. (As this is exploratory research, the hypothesis is non-directional).

This design requires statistical analysis by means of 2-way analysis of variance with repeated measures on the trials variable, thus systematic differences in test scores after 8 weeks and after 16 weeks, as functions of differential effects of treatments, can only be detected through significant interaction effects. Consequently, the null hypothesis can be stated as follows:

3.2 NULL HYPOTHESIS

There is no significant effect of interaction between the effects of treatment sequence and the trials variable on psychometric performance of abstinent chronic alcoholics.

4. METHOD

4.1 DESIGN

A placebo-controlled, randomised double-blind crossover design was used, with three assessments on the battery test. These assessments occurred for each subject at:

(i) baseline
(ii) after 8 weeks of treatment
(iii) after 16 weeks of treatment

Group 1 received placebo treatment for a first 8 week period, followed by a crossover to piracetam for a further 8 weeks. Group 2 received piracetam for 8 weeks followed by placebo for a further 8 weeks. Subjects selected for the trial were randomly allocated to one of the two treatment groups as they entered the trial. The manipulated variable was drug treatment, which was varied along the trials variable, while the dependent variable was psychometric performance, represented by a wide range of psychological functions. Each pyschological function was statistically analysed separately.

4.2 SUBJECTS

All subjects in this study had received treatment for chronic alcoholism at the William Slater Hospital, Rondebosch, Cape, and all but three were still receiving outpatient treatment from this same institution. The remaining three subjects maintained contact with the hospital through attending meetings of Alcoholics Anonymous on the premises. The hospital was chosen as a convenient facility specialising in the treatment of alcoholism and possessing a large pool of potential subjects.

Hospital staff checked hospital records to identify possible subjects, both White males and White females, according to the following criteria:

(a) aged between 35 and 60 years
(b) an estimated duration of problem drinking of at least 10 years

(c) apparent absence of problem drinking for at least 3 months.

(d) having a record of reliability, in terms of regular adherence to hospital appointments and of maintaining contact with the hospital.

(The three subjects who were not outpatients were known to have good records of attendance at AA meetings on the premises).

Potential subjects were excluded on the following criteria:

(a) presence of psychotic illness, including the Wernicke-Korsakoff syndrome.

(b) presence of serious physical disease.

One hundred and twenty-three eligible patients were approached, of whom 63 eventually participated. Of these, eight were female. The mean age of the entire sample at the commencement of the trial (years only) was 48,01 with a sustained deviation of 6,99 years.

An estimate of the length of history of problem drinking, based on hospital records and questioning of subjects, yielded a mean duration of 20,84 years, with a standard deviation of 7,37 years.

4.3 TREATMENT MATERIALS

Tablets for both piracetam and placebo treatments were idential in size, colour and overall appearance and were packed in quantities of 168 in identical metal canisters. Each canister contained a supply sufficient for exactly 4 weeks of treatment.

There were four canisters per subject, two each of piracetam and two of placebo, each subject 's supply being separately boxed. Each canister bore the subject 's number and the period of the trial for which it was intended, ie - Per 1 (period 1) or Per 11 (period 11). In addition, each box contained a sealed, opaque envelope containing the treatment sequence data. This envelope was not opened until the end of the trial and after scoring had been completed for all subjects.

4.4 PHYSICAL APPARATUS

The only non-standard apparatus used was an electronic reaction timer, assessing three-choice visual reaction time. This apparatus consisted of two units, an impulse generator and a unit housing the response and measurement consoles. The response console housed three response keys (one per light) and a 'starting' key, plus red, green and yellow stimulus lights. The measurement console consisted of a digital display registering milliseconds and a 'reset' button. At one side was a switch inverting the red and green lights' response circuits for the 'reversed' reaction timing condition. (For a fuller description see Appendices 1 and 2).

4.5 TESTS

4.5.1 Choice Reaction Time

Choice Reaction Time (CRT) was chosen as a measure of psychomotor performance which is considered an index of attentional monitoring, far more so than Simple Reaction Time, which is much less reliant on central processes. CRT has been used frequently in drug research and has proved its sensitivity to a wide range of psychotropic substances (Hindmarch, 1980). Once the effects of practice have stabilised, the latency of response is dependent on the number of possible responses (Teichner & Krebs, 1974).

Talland (1963) found alcoholics deficient relative to controls in all forms of Reaction Time that he tested. Bente (1977) has argued that piracetam probably acts to rectify impairments in vigilance regulatory mechanisms. Consequently, it appears that CRT might be the most powerful means of detecting these changes. Three-Choice Reaction Time was chosen as a sufficiently complex means of assessment, capable of offering chronic alcoholics large opportunities to demonstrate improvements under the influence of piracetam.

In addition to CRT, it was considered possible to evaluate the effects of change of set on this variable by means of reversing response keys

such that for certain stimuli the responses required had to be changed. This has been done with two-choice reaction time (Lagergren & Levander, (1974).

Change of mental set has been demonstrated, in studies of alcoholics on the Wisconsin Card Sorting Test, to increase the number of errors made (Tarter & Parsons, 1971; Tarter, 1973). Consequently, it was expected that the required alterations in responses to the same stimuli would result in greater latencies of response which would fluctuate as a function of piracetam or placebo treatment.

As there were three response keys, the alteration of responses could have resulted in very complicated instruction in the reversed condition, as at least one stimulus light-response key relationship would have to change in the opposite direction to the other two, if all three relationships were to change. It was thus decided to reverse the relationships between the left (red), and right (green), keys and stimuli, leaving the key-to-light stimulus relationship in the middle (yellow) as it was. This condition was called the 'reversed condition' and the former the 'standard condition.'

Subjects were given ten practice trials in each condition, followed by 30 test trials which were measured. The mean of the 30 trials was one performance measure, but this was broken down to allow comparison of the responses to red and green stimuli in the two conditions. The sequence of stimulus onsets was standard and randomly programmed, including in the test stimuli, 10 stimuli of each colour. (For further details of apparatus and procedure, see Appendices 1, 2 and 3).

4.5.2 Purdue Pegboard

This is a test of motor manipulative ability, which has been shown sensitive to centrally acting drugs (Hindmarch, 1980). Vaughan and Costa (1962) attempted to use the Purdue Pegboard to discriminate between lesions in the left and right hemispheres, but their data forced them to conclude that the "physiologic system underlying

performance on the Purdue Pegboard appears to be relatively diffuse. It is related to systems subserving both motor and somesthetic functions" (p. 242). In a later study Costa et al. (1963) using a short form were able to identify 93% of a sample of 80 consecutive referrals to a neurological clinic in terms of presence or absence of brain damage. Generally, the brain-damaged group scored lower than those who were adjudged on neurological, EEG and neuroradiological grounds as normal. Utilised later, it correctly identified 95% of referrals. This suggests that chronic alcoholics should score poorly on this test.

The short form utilises 30-second trials during which the subject must place as many pins as he can, one at a time, in a row of holes set in a wooden board. Trials are conducted separately with the dominant and non-dominant hands, and then with both hands simultaneously. Standard instructions were given to the subjects from the manual (Tiffin, 1968).

4.5.3 Wechsler Adult Intelligence Scale Sub-tests

4.5.3.1 Information Sub-test:

This is a test of long term memory (Maloney & Ward, 1974), loading on a general verbal comprehension factor (Anastasi, 1968). According to Lezak (1976), it is also influenced by mental alertness. The test is known to be a 'hold' test, but bearing in mind the equivocal nature of certain results relating to the general invulnerability of verbal skills in alcoholics (Fitz-Hugh et al.,1965; Grant et al., 1979; Adams et al., 1980 and Ron, 1982), it was decide to include it. Another reason for its inclusion was that its presence would permit an approximation of Full Scale IQ based on equal numbers of verbal and performance sub-tests.

4.5.3.2 Digit Span Sub-test:

This assesses auditory rote (short term) memory and is susceptible to the effects of disturbances in attention and concentration (Maloney & Ward, 1976). Lezak (1976) claims it

is a good indicator of diffuse brain damage. Certainly, memory deficits are very commonly reported in chronic alcoholic populations (Kaszniak, 1975; Lezak, 1976; Lee et al., 1979; Ryan, 1980) and this test was chosen to assess possible improvements on these functions as a result of piracetam treatment.

Griffin and Hefferman (1983) found that separating the 'Digits Forwards' and 'Digits Backwards' sections of this test resulted in differing relationships to global intellectual functioning, with the latter bearing a much greater relationship to this. They postulated that 'Digits Backwards' required a degree of 'double tracking,' that is, holding an item whilst simultaneously manipulating it, while 'Digits Forwards' measured pure rote memory. It was decided to analyse results according to overall 'Digit Span' and by the two sub-sections, in the expectation that the complexity of 'Digits Backwards' would make it more sensitive to disturbances of attention and concentration. This methodology has been successfully used in the study of acute intoxication effects in the past by Melges et al. (1970).

This test has advantages in terms of speed of completion and simplicity of administration.

4.5.3.3 Similarities Sub-test:

Kleinknecht and Goldstein (1972) and Wechsler (1958) have reported consistent deficits in chronic alcoholics on the Similarities sub-test. It is, primarily, a test of abstract thought and verbal concept formation and, to an extent, involves remote memory, comprehension and associative thought (Maloney & Ward, 1976). Lezak (1976) claims that this test is most sensitive to damage to the frontal lobes of the brain, but is sensitive also to all other forms of brain damage.

4.5.3.4 Object Assembly Sub-test:

A visual-motor performance sub-test, Object Assembly is said to be sensitive to perceptual deficits (Maloney & Ward, 1976), and scores reflect perception of wholes and rapidity of recognition in particular (Matarazzo, 1972). In their review of the utility of WAIS sub-tests in assessing chronic alcoholics' functional deficits, Kleinknecht and Goldstein (1972) report Object Assembly as the most commonly reported test registering alcoholic deficits, along with Digit Symbol Substitution. More recently this has been supported by findings from Long and MacLachlan (1974) and O'Leary et al. (1979).

4.5.3.5 Block Design Sub-test:

Performance on the Block Design Sub-test reflects non-verbal concept formation, and depends on perceptual-motor integration and sustained effort (Maloney & Ward, 1976). Matarazzo (1972) reviewed literature indicating poor performance to be associated with frontal lobe atrophy, but Lezak (1976) argues that this test reflects any form of brain damage.

Recent studies that have found poorer performance in alcoholic groups are Long and MacLachlan (1974), MacLachlan and Levinson (1974) and O'Leary et al. (1979).

4.5.3.6 Digit Symbol Substitution Sub-test:

Kleinknecht and Goldstein (1972), reviewing the literature of use of the WAIS in chronic alcoholic populations, concluded that Object Assembly and Digit Symbol Substitution were the most consistently reported tests upon which alcoholics were reported deficient. Maloney and Ward (1976) assert that performance depends upon eye-hand co-ordination, concentration, immediate memory and psychomotor speed, but the factor most frequently mentioned by other authorities is concentration or attention (Matarazzo, 1972; Lezak, 1976).

On aggregate, Digit Symbol Substitution provides an assessment of sensory processing ability. Hindmarch (1980) reviewed literature on drug trials and was able to show that this test is very sensitive to drug effects when these relate to central processes. Hindmarch admitted that there is a motor component to the task but he concluded that the principal determinant of results was the recoding of visual information.

4.5.4 Modified Card Sorting Test

The Wisconsin Card Sorting Test (WCST) may be classified as a psychomotor test (Hindmarch, 1980) where the motor aspect is of minimal importance and the emphasis falls on central processes. It is primarily a test of abstract thought,concentration and difficulty in changing mental set (Ron, 1982), and provides a strong evaluation of perseverative tendencies.

Kleinknecht and Goldstein (1972) concluded that one of the areas in which alcoholics were deficient was in abstract reasoning and problem solving. This conclusion was largely based on consistently reported alcoholic deficits on the Category Test of the Halstead-Retan Neuropsychological Battery, a test which is generally regarded as tapping the same functions as the WCST. Abstract thought and perseverative tendencies are most related to the frontal lobes (Lezak, 1976).

Nelson (1976) modified the WCST because feedback on correct responses could be ambiguous, in that a card matched to a key card could be correct for either of two reasons in certain cases. She reduced the number of sorting cards from 64 to 48, eliminating those cards responsible for the ambiguity. The number of correct "sorts" in a continuous sequence was reduced from 10 to 6, effectively reducing the administration time.

Scoring of errors was unchanged, but the method of scoring "perseverative" errors was altered. A perserverative error was previously regarded as a response which conformed to the set used prior to the current set. However, Nelson (1976) re-defined a perseverative error to denote one which was preceded by another error, and was made according to the same set as

that previous error. (For details of administration procedures, see Appendix 4).

Ron (1982) used Nelson's Modified Card Sorting Test, finding that total errors discriminated chronic alcoholics from controls. This supported an earlier finding by Tarter and Parsons (1971). Other studies supporting the utility of the WCST in the study of chronic alcoholics are Tarter (1971), Klisz and Parsons (1979) and Parker and Noble (1980).

4.5.5 'Selective' & 'Restrictive' Reminding in List Learning

Buschke (1973) and Buschke and Fuld (1974) have developed methods of analysing free recall over repeated trials to determine long term storage (LTS) and retrieval (LTR) as well as short term retrieval (STR). They argued that traditional free recall experiments in which an entire list of words is presented before each recall attempt do not permit distinctions between the contributions of long term memory and rote memory.

"Selective Reminding" involved reminding before a recall attempt of all items not recalled in the previous recall attempt, while "Restricted Reminding" limited reminding to words not yet recalled on any prior recall attempt. While the former condition allows maximum opportunity to demonstrate learning, the latter might result in lower total recall scores but will provide a more stringent assessment of retrieval function uncontaminated by STR. Buschke and Fuld (1976) presented alcoholic case study data indicative of defective retrieval operations, as LTS had been demonstrated but LTR could not measure up to this.

On time considerations, it was not possible to replicate the Buschke and Fuld methodology which frequently involved more than ten recall attempts. It was therefore decided to limit recall trials to three, and to take LTR at trial three as both an adequate demonstration of retrieval and as an approximation of LTS, though this latter will usually be an underestimate, at best equal to LTR. The major emphasis fell on adequacy of retrieval. Buschke and Fuld argued that little of the retrieval in the case study material was consistent, the balance being random and disorganized. The inconsistent nature of retrieval argues for deficient organized search procedures, which should respond to centrally active drugs acting on higher integrative and associative mechanisms. Improvements in organized search procedures should reflect themselves in increasing LTR.

Both methods assess retrieval, the latter more so. Selective Reminding also provides an estimate of learning ability. Overall scores of the three recall trials were used to assess the amount of learning which took place.

Test materials consisted of three equivalent-difficulty lists of 20 words, one for each assessment for each condition, yielding a total of six. All words used were nouns. For instructions to subjects, and list information, see Appendices 5 and 6.

4.5.6 Serial 3s

Serial subtraction of numbers has been used as a measure of attention and concentration extensively in drug trials (Hindmarch, 1980). It can be scored on time or errors(Lezak, 1976) and is very easily applied. It has been noted by Lezak that problems on this test are both more frequent and of greater magnitude in brain damaged populations than in others.

It was decided to standardize the time of this test at 30 seconds, and to score according to errors, number of items correctly enumerated within the time limits, and total number of items enumerated. All three forms of scoring were adopted to check against each other as different test-taking styles might bias any one analysis.

Three forms were used, starting at 100, 99, and 98 respectively.

4.5.7 Inglis Paired Associate Learning Test

Inglis (1959) claims this test is most sensitive to the encoding phase of learning, and is independent of age and intelligence. It is a test of auditory verbal recall originally designed for use in the elderly populations. Inglis (1959) and Caird et al. (1962) claimed it useful in identifying memory-disordered patients. This type of task has been shown sensitive to alcoholic brain impairment (Acker, 1982).

Paired associate learning tests are regarded as sensitive to drug effects, and as chronic alcoholics have long been regarded as possessing their primary deficit in memory, this test was chosen.

The test has two forms, each of three pairs of words. A third form, required for assessment three, was developed by Oblowitz (1982) and was matched to the former two forms in abstractness-concreteness, imagery and word association values, as well as Thorndike-Lorge noun frequency. (See Appendices 8 and 9).

The subjects are initially presented with the three noun pairs at five second intervals and are then presented with the initial noun of the pair and are asked to provide the associate. Immediate feedback is given. Initial nouns are randomly alternated in presentation until pairs are dropped when three consecutive presentations meet with the correct response. Scoring is in terms of total presentations required to either the meeting of criterion for the third pair, or 93, if the criteria cannot be met. Initial presentation of the noun pairs is included, yielding a minimum score of 3.

4.5.8 Hamilton Psychiatric Rating Scale for Depression

Kabes et al. (1979) reported that piracetam exerted beneficial effects on drug-resistant depression. As alcoholic populations are frequently reported as containing many depressed individuals, it was considered desirable to include an instrument to assess this variable, as any

systematic anti-depressant effect could exert an influence on test performance and, consequently, contaminate the findings of the study.

The Hamilton Psychiatric Rating Scale for Depression consists of 17 items, yielding a maximum (most depressed) score of 50 and a minimum of 0 (not depressed). The scale items assess the presence and severity of depressive symptomatology. All rating is done by the experimenter.

For the sake of brevity, this scale is hereafter referred to as the 'Hamilton Depression Scale' or 'HDS.' (See Apendix 10 for questionnaire).

4.6 PROCEDURE

Hospital staff identified potential subjects from hospital records, using the criteria referred to above under 'Subjects.' These patients were then approached by mail and invited to participate in the trial (see Appendix 11). These patients were asked to contact the hospital and, if interested in participating, an appointment was made to see either Dr I Fraser, the consultant, or, after his departure from the hospital, Dr A Robins of the Department of Pharmacology, University of Cape Town.

At this interview the patient's medical history was updated, as were the details of current medications. Patients were informed that the long term administration of alcohol was known to affect memory and other cognitive functions adversely, and that the drug under consideration, piracetam, was considered as likely to be of benefit in combating these problems. It was further explained that the drug was considered to be perfectly safe, that no side effects were known, that no interactive effects with other drugs had been observed, and that the study had been approved by the Ethical Review Committee of the University of Cape Town Medical School.

Patients were informed that the trial would require their being assessed

on a battery of tests on three occasions, at 8 week intervals, and that they would be required to take medication daily for a total of 16 weeks. Those patients who agreed to participate then signed an informed consent (see Appendix 12) and an appointment was made for baseline assessment.

At baseline assessment clinical data relating to alcohol abuse and medication were gathered, as well as personal details considered relevant to contacting subjects in the event of difficulties (see Appendix 13). Subjects were informed that they would be given some qualitative feedback after termination of the trial. They were also assured of the confidentiality of all that transpired at assessments, and were instructed that all unconsumed tablets must be returned at each subsequent assessment, and that they were not to discuss the research, medication or test content in any way. Finally, subjects were required to report any changes in medication during the trial and, as far as possible, to avoid such changes. Subjects were given a note to their doctors to this effect (see Appendix 14).

Tests were then presented in the following order:

1. Hamiltons Psychiatric Rating Scale for Depression
2. Choice Reaction Time
3. Purdue Pegboard
4. WAIS (a) Information
   (b) Digit Span
   (c) Similarities
   (d) Object Assembly
   (e) Block Design
   (f) Digit Symbol Substitution
5. Modified Card Sorting Test
6. List Learning-Selective Reminding
7. Serial 3s
8. List Learning-Restrictive Reminding
9. Inglis Paired Associate Learning Test

All tests were administered according to standard procedures, where these existed. Procedures and instructions had to be formulated for

Reaction Time, List Learning and Serial 3s (see Appendices 3, 5 and 7).

On completion of the test battery, the subject was given a 4 week supply of tablets for Period 1 of the trial, from the subject's respective medical supply and instructed to make arrangements to collect the second canister before the first supply was exhausted. Each subject was instructed to take two tablets three times daily, ie - 4,8gm/day, for convenience, preferably at mealtimes.

The date of the second assessment was set at exactly 8 weeks from the date of baseline assessment and, as far as possible, for the same time of day. The same procedure was followed in setting the date of the third assessment.

At subsequent assessments the battery was applied in the same order, with equivalent forms substituted in the cases of List Learning, Serial 3s and Inglis Paired Associate Learning Test. Tablet returns were counted and new supplies issued at the second assessment and data concerning possible side effects and any changes in other medications were gathered. Where subjects omitted to return unused pills, they were asked to put these aside, not to use any and to return these for counting as soon as possible.

Between assessments replacement supplies of medications were distributed either directly at arranged times, or through the hospital's outpatient medication distribution system, where the subjects could not pick these up during the day. The latter was the more common means of distribution.

No scoring was done until all subjects had completed the trial, and all potentially useful means of scoring were employed before the codes were broken and the data were grouped for statistical analysis. Exclusion criteria were only operated upon after all subjects (excluding dropouts) had completed the trial (see Appendix 15).

4.7 SCORING

All scores used, with the exception of pro-rated WAIS IQ scores, were raw scores, including those on the WAIS sub-tests. It was considered that these WAIS sub-tests were primarily evaluated as assessments of group functions and that standardisation of these scores would serve no useful purpose but, on the contrary, lead to loss of fine discrimination by reducing the range of scores.

Although it is frequently claimed that individual sub-test scores are unreliable, the danger in interpreting these is greatest for individual cases. When data are grouped, however, fluctuations might reasonably be expected to average out.

4.8 STATISTICAL ANALYSIS

The data were analysed by means of two-way anovas with repeated measures on the B factor. Factor A was the drug sequence variable for which there were two levels: the placebo-piracetam sequence ($A\overline{1}$) and the piracetam-placebo sequence ($A\overline{11}$). Factor B was a trials (time of assessment) factor for which there were three levels: baseline (B1), crossover (B2) and termination (B3), corresponding to weeks 0, 8 and 16.

As subjects were randomly assigned to treatment groups, and as piracetam is not known to have long term after-effects, sequence effects were not expected to emerge.

The two-way anova with repeated measures on the trials factor is, however, very sensitive to effects in the trials factor, and these were expected in many analyses in the event of interactive effects not being found (Gilbert, 1977).

Differing effects of piracetam and placebo could only be considered to have emerged when interaction became significant. In any other eventuality, the statistic allowed no conclusions to be drawn concerning

differential treatment effects of placebo and piracetam.

A basic assumption of the analysis of variance is that of homogeneity of variance which, if violated, casts doubt as to the correctness of the value of the error variance which, in turn, implicates obtained F-values for interaction and B main effects in the case of violated *residual* error variance, and A main effects in the event of violation of subject error variance.

Such violations can arise when the independent variable involves time, error scores or changes to or from an extreme (Gilbert, 1977). In the case of the present battery, this appears more applicable to the unstandardised methods of assessment, particularly the Modified Card Sorting Test and Serial 3s, but also possibly the Purdue Pegboard, List Learning Tasks and Inglis Paired Associate Learning Test, where the possibilities of large movements towards or away from extreme scores cannot be ruled out.

In the event of such violations of F max, there are several means of correction available. Transformation scores are the best means of eliminating F max violations, but involve serious limitations in subsequent interpretability. Degrees of freedom may be divided by an arbitrary figure to make attainment of statistical significance more difficult, or a higher level of significance may be used, which also makes for a more stringent test.

Use of a higher level of significance is the most practical solution and for any F max violations, a level of significance of $p \leqslant ,01$ was used. This was not unduly strict, as the abundance of F values in the subsequent data enhanced the possibility of Type 1 errors, that is, of significance being attached to purely chance events.

5. RESULTS

5.1 DESCRIPTIVE STATISTICS

TABLE 1 Descriptive Parameters of Original and Final Total Samples

	Original Sample	Final Sample
Number of subjects	63	48
Number of male Ss	55	40
Number of female Sa	8	8
Mean age (years)	48,01 (6,99*)	48,00 (6,73*)
Estimated mean drinking history (years)	20,84 (7,37*)	20,79 (7,22*)

* Standard deviation

Sixty three subjects commenced the trial, and 57 completed the three assessments, of whom a further 9 were excluded on grounds of inadequate compliance to the treatment regime in terms of consumption of "medications" or extreme deviance from prescribed inter-assessment intervals (see Appendix 15).

Eight subjects in the original sample were female, and all were included in the final sample. All drop-outs and exclusions were thus male.

The two samples mean ages, as at baseline assessment, are extremely similar, being 48,01 years in the original sample, and 48,00 years in the final sample. Similarly, values for estimated mean drinking histories are practically identical, being 20,84 years in the original sanple and 20,79 in the final sample.

These values (see Table 1) are so highly related that statistical evaluation is considered irrelevant. The small magnitude of these differences are unlikely to be of practical significance.

TABLE 2 Details of Treatment Group Sizes, Composition by Sex and Mean Ages and Drinking History Values (standard deviations in brackets)

Treatment Group	Group 1 (Placebo-Piracetam)	Group 2 (Piracetam-Placebo)
Initial number of subjects	33	30
Final number of subjects	26	22
Number of males in final group	18	22
Number of females in final group	8	0
Final group mean age (years)	47,65 (6,78*)	48,41 (6,84*)
Final group mean drinking history (years)	19,12 (6,88*)	22,09 (7,10*)

* Standard deviation

Table 2 contains details of the two treatment groups. The groups differ significantly in composition by sex (chi-squared test of association = 6,06; df = 1; $p < ,05$) despite random allocation to groups. However the groups do not differ significantly on age ($t = 1,20$; df = 46; n.s.) nor on mean drinking history ($t = -1,47$; df = 46; n.s.).

Rates of subject attition did not differ across the two groups (Chi-squared test of association = 0,04; df = 1; n.s.). Consequently it may be concluded that the two groups are comparable on all but composition by sex. This latter is a chance result. Information concerning drop-outs and exclusions can be found in Appendix 15. (Additional subject information is presented in Appendices 16 to 17).

5.2 Two Way Analyses of Variance with Repeated Measures of Factor B

All statistical analyses utilized data from the final sample alone. Separate analyses are presented for each test or scoring method employed. Raw scores may be found in Appendix 20.

In all the following analyses, for the sake of brevity the treatment

sequences will be referred to as Sequence 1, indicating placebo preceding piracetam, and Sequence 2, indicating piracetam preceding placebo. Sequence 1 is synonymous with level AI of Factor A (the Groups Factor), and Sequence 2 is synonymous with the level AII of the Groups Factor.

In addition, in all tables of cell means, bracketed figures behind the cell means indicate the standard deviation of scores in those cells. Any tabled F-values without probability values are not significant.

Although interassessment intervals were not always rigidly kept at eight weeks, for simplicity in tables and figures, the levels of Factor B (trials) are described as "Baseline", "After 8 weeks" and "After 16 weeks".

TABLE 3 Mean Hamilton Depression Scale (HDS) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	16,08 (12,94)	11,62 (10,92)	12,46 (7,32)
Sequence 2 (A2)	14,54 (10,66)	11,64 (8,58)	14,46 (9,74)

The mean depression scores of the two groups at each assessment are presented in Table 3, and illustrated in Figure 2. A drop of depression scores, indicating improvement, is evident after 8 weeks in both groups, but this is reversed in both, though only partially in the group receiving piracetam prior to assessment, at week 16.

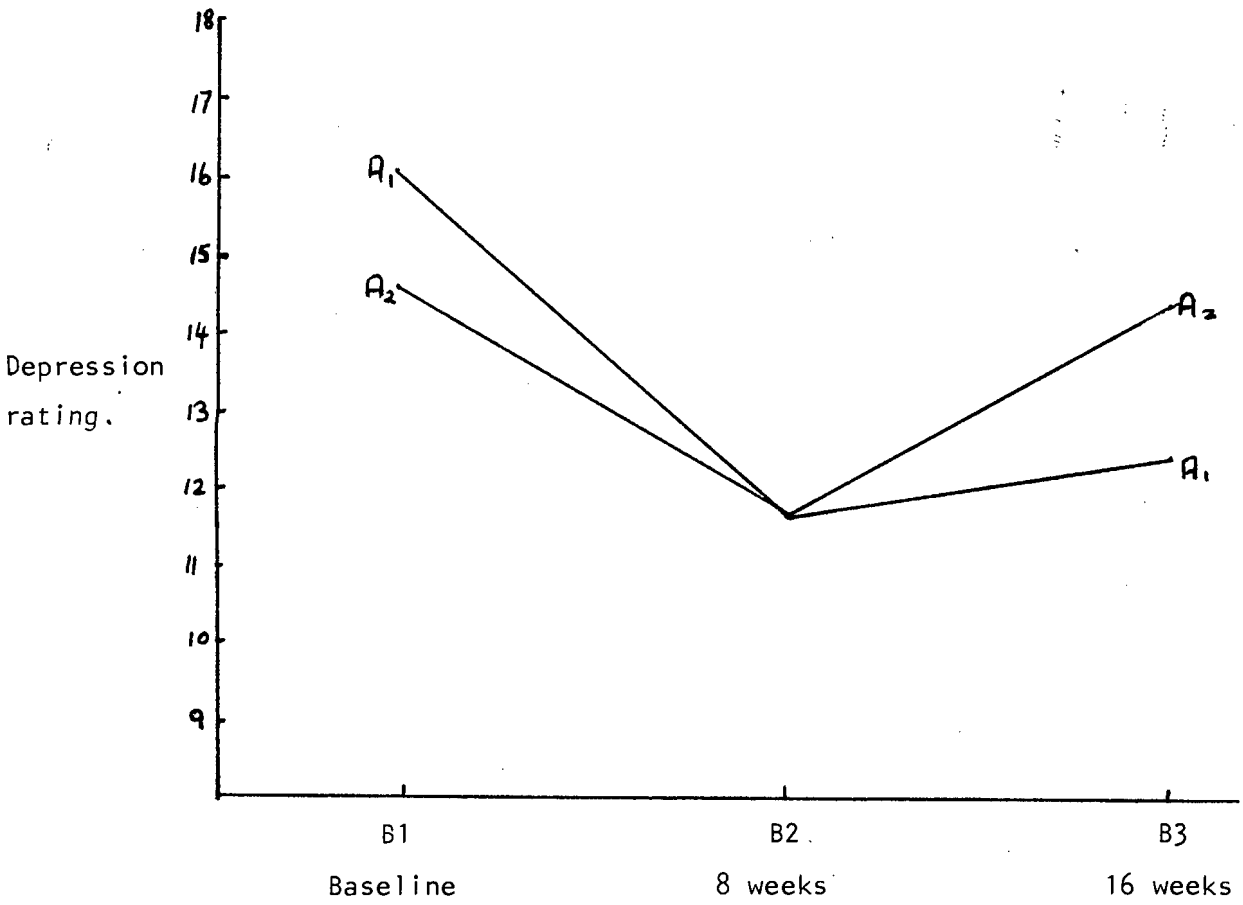


FIGURE 2:Hamilton Depression Scale Cell Mean Profile.

The cell mean profile indicates different trends for the groups. These are assessed for statistical significance by a two-way analysis of variance with repeated measures on Factor B, the results of which are presented in Table 4.

There is no significant interaction effect, nor is there a significant A (sequence) main effect. The B (trials) main effect is significant ($p < ,05$), requiring further investigation using Tukey HSD analysis. These results are presented in Table 5.

TABLE 4 Anova Summary Table for Hamiltons Depression Scale Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,23	0,00
Subjects	46	59,99	
Within subjects			
B. Time of assessment	2	40,46	4,38 ($p < ,05$)
AB. Interaction	2	9,30	1,01
Residual	92	9,24	

TABLE 5 Tukey HSD Results for HDS Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	4,18 ($p < ,05$)	2,11
After 8 weeks		-2,07

The results shown in Table 5 indicate that the significant B (trials) main effect is due entirely to the improvement in scores between baseline and the second assessment ($p < ,05$). This improvement occurs irrespective of the substance administered between these assessments, and argues for an unsustained placebo effect.

5.2.2.1 Overall Mean Choice Reaction Time (CRT) Scores Under Standard Conditions

Mean scores for all reaction times measured (up to 30) under standard conditions are presented in Table 6, and illustrated in Figure 3. Differing trends are noticeable in the first half of the trial, but not in the second, although the decrease (improvement) in Sequence 2 subjects' scores is more marked.

TABLE 6 Mean Choice Reaction Time (CRT) under Standard Conditions (milliseconds)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	711,77 (117,17)	715,96 (119,78)	682,54 (148,89)
Sequence 2 (A2)	683,00 (110,35)	712,41 (126,97)	657,68 (106,59)

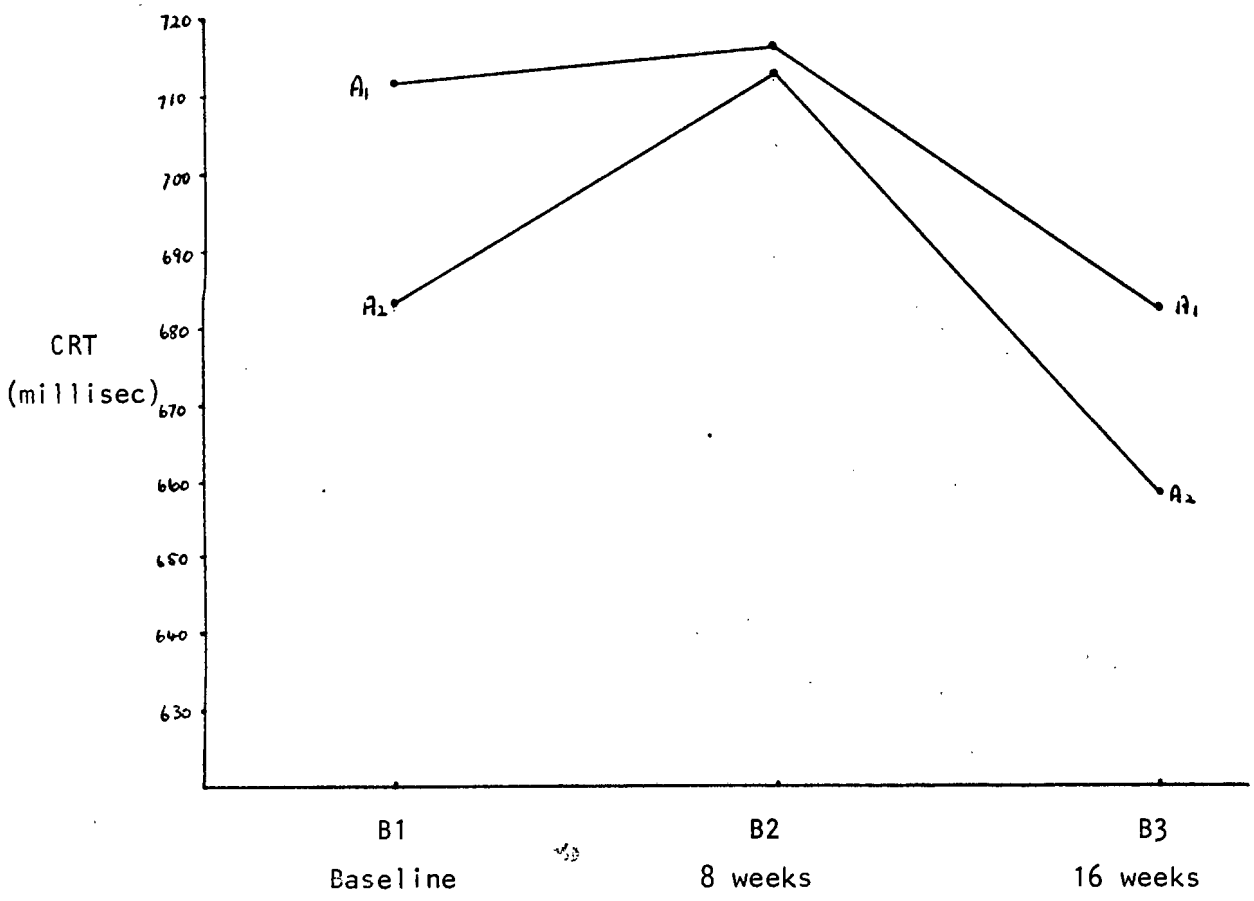


FIGURE 3: Choice Reaction Time (Standard Condition Overall Means) Cell Mean Profile.

Results of the evaluation of the trends in the data by means of two way analysis of variance with repeated measures on the B Factor are recorded in Table 7. Neither interaction effects nor main effects are significant, and no further analysis is possible.

TABLE 7 Anova Summary Table For CRT Scores under Standard Conditions

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	12987,68	0,62
Subjects	46	20919,15	
Within subjects			
B. Time of assessment	2	23586,81	1,95
AB. Interaction	2	2193,78	0,18
Residual	92	12246,89	

5.2.2.2 Overall Mean CRT Scores Under Reversed Conditions

Table 8 presents mean scores for all response latencies (up to 30) measured under reversed conditions, i.e., when the responses required to terminate two lights were interchanged compared to the standard condition.

TABLE 8 Mean CRT under Reversed Conditions (milliseconds)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	806,92 (132,61)	761,50 (106,28)	724,31 (88,44)
Sequence 2 (A2)	799,50 (134,41)	738,91 (91,51)	740,18 (98,46)

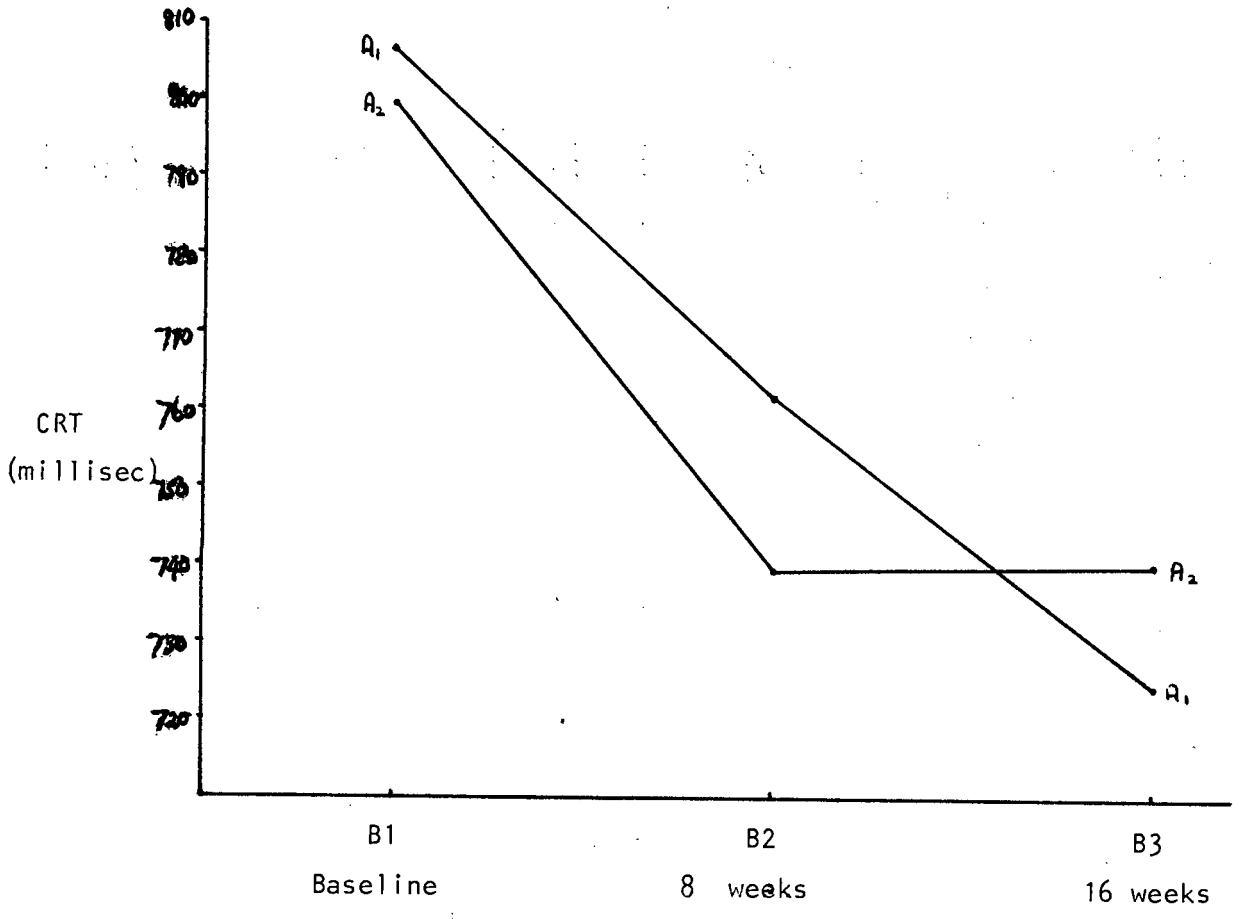


FIGURE 4: Choice Reaction Time (Reversed Condition Overall Means) Cell Mean Profile.

The trend of scores as shown in Figure 4 is the same in both groups, for the first trial period, a marked improvement being observed. However, in the second trial period, the improvement is sustained by Sequence 1 subjects but improvement levels off for the other group.

The analysis of the above trends is found in Table 9. Despite the apparent trends in Figure 4, no significant interaction is observed. The main effect for treatment sequence is also not significant, but the B main effect (trials) is highly significant ($p < ,01$) and requires further analysis by means of Tukey HSD statistics. The results of these are seen in Table 10.

TABLE 9 Anova Summary Table for CRT Scores under Reversed Conditions

Source	df	MS	F ratio
Between subjects	1	795,44	0,03
A. Treatment sequence	46	29068,07	
Subjects			
Within subjects			
B. Time of assessment	2	64895,93	17,60 ($p < ,01$)
AB. Interaction	2	4472,47	1,21
Residual	92	3687,92	

TABLE 10 Tukey HSD Results for CRT Overall Means at Each Assessment under Reversed Conditions

	After 8 weeks	After 16 weeks
Baseline (B1)	6,04 ($p < ,01$)	8,09 ($p < ,01$)
After 8 weeks (B2)		2,05

The Tukeys analyses clearly separate the baseline scores from the later scores (both $p < ,01$) which do not differ between themselves. Clearly this reflects the large improvement noted between baseline and the second assessment on Figure 4, which is maintained to a lesser extent in the second trial period when the results of the two treatment groups are considered together.

5.2.2.3 Mean CRT Scores Under Standard Conditions: Yellow (central) Stimuli Alone.

Mean scores of the two treatment groups at the three times of assessment for response latency related to yellow, or central, stimuli are recorded in Table 11, and illustrated in Figure 5.

TABLE 11 Mean CRT for Yellow Stimuli under Standard Conditions (milliseconds)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	710,96 (132,97)	775,39 (284,91)	728,73 (279,17)
Sequence 2 (A2)	699,41 (143,67)	763,46 (244,70)	694,82 (163,09)

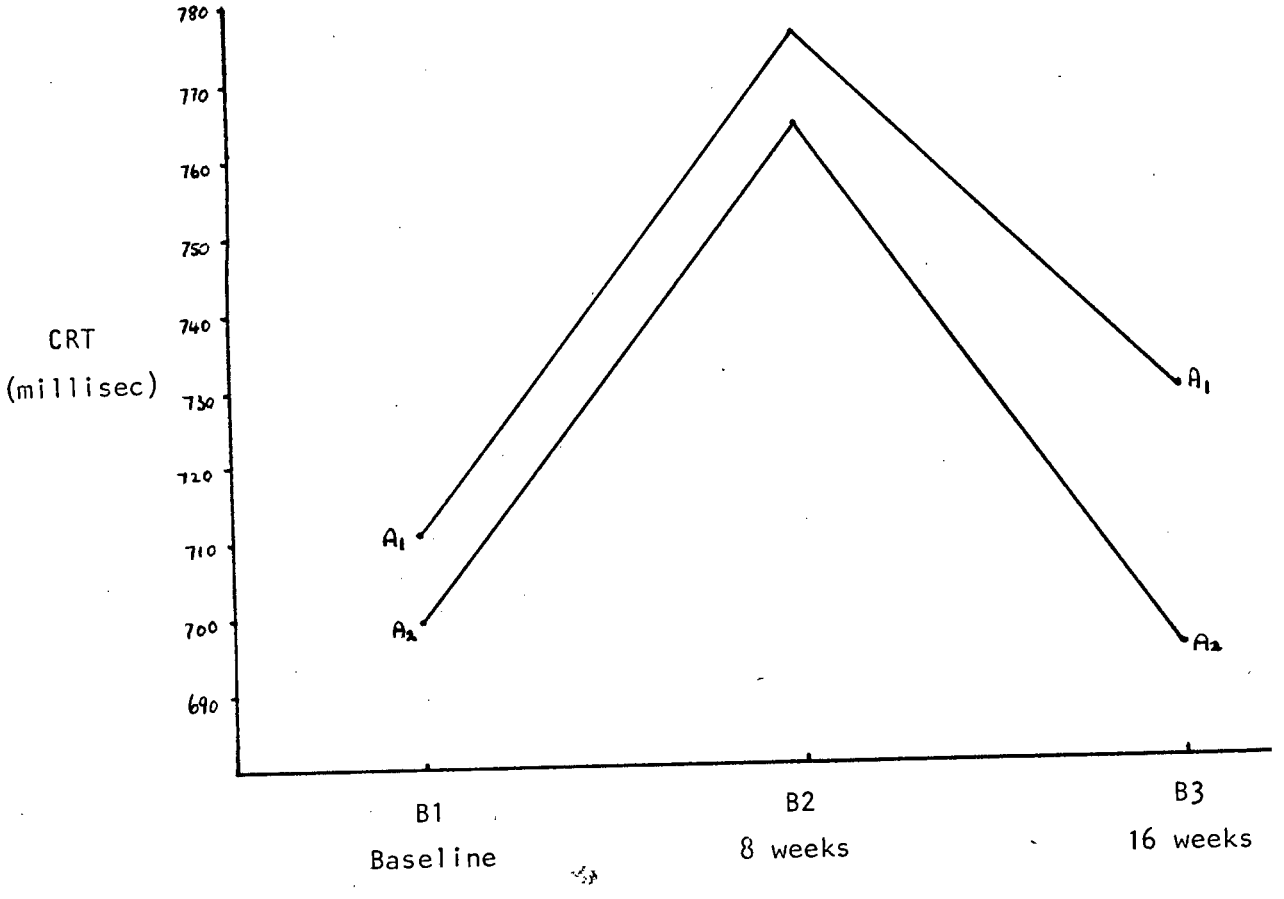


FIGURE 5: Choice Reaction Time (Standard Condition Yellow Stimuli) Cell Mean Profile.

The mean scores of subjects receiving Sequence I are always higher than the mean scores of the other group. However, the trends are, with minor deviations, parallel. Large increases in CRT are observed after 8 weeks, with a return to baseline at 16 weeks.

Results of statistical analysis are presented in Table 12.

TABLE 12 Anova Summary Table for CRT for Yellow Stimuli under Standard Conditions

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	13085,99	0,22
Subjects	46	59222,33	
Within subjects			
B. Time of assessment	2	59523,75	1,39
AB. Interaction	2	1952,10	0,05
Residual	92	42879,89	

No significant effects were detected in this analysis, despite the large deterioration in scores after 8 weeks, and thus no conclusions can be drawn as to any systematic variations in the data. However, homogeneity of residual variance was violated in this analysis ($F_{max} = 2,32$; $df = 2$ and 44; $p < ,05$). Subject variance was not violated.

Use of a higher level of significance to correct for the violation of F max residual does not change the above conclusions of no significant effects.

5.2.2.4 Mean CRT Scores Under Reversed Conditions: Yellow (central) Stimuli Alone.

TABLE 13 Mean CRT for Yellow Stimuli under Reversed Conditions (milliseconds)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	756,46 (97,12)	701,19 (93,01)	654,23 (84,41)
Sequence 2 (A2)	738,05 (96,11)	705,77 (89,89)	683,05 (97,07)

Mean values obtained for CRT for yellow stimuli alone, under reversed conditions, are presented in Table 13 and illustrated in Figure 6. It is clear that in both groups the CRT scores decrease over time and that Sequence 1 subjects show consistently greater improvement over the two trial periods than do Sequence 2 subjects. In both groups the amount of improvement shown is approximately equal for each trial period.

Assessments of statistical significance of the trends in this data are presented in Table 14. The only result to achieve significance is the trials main effect ($p < ,01$). The results of Tukey HSD analysis of this main effect are presented in Table 15. All comparisons are significant at $p < ,01$. The mean score at baseline is significantly greater than mean scores after 8 and 16 weeks (both $p < ,01$) and the mean score after 8 weeks is significantly greater than the mean score after 16 weeks ($p < ,01$).

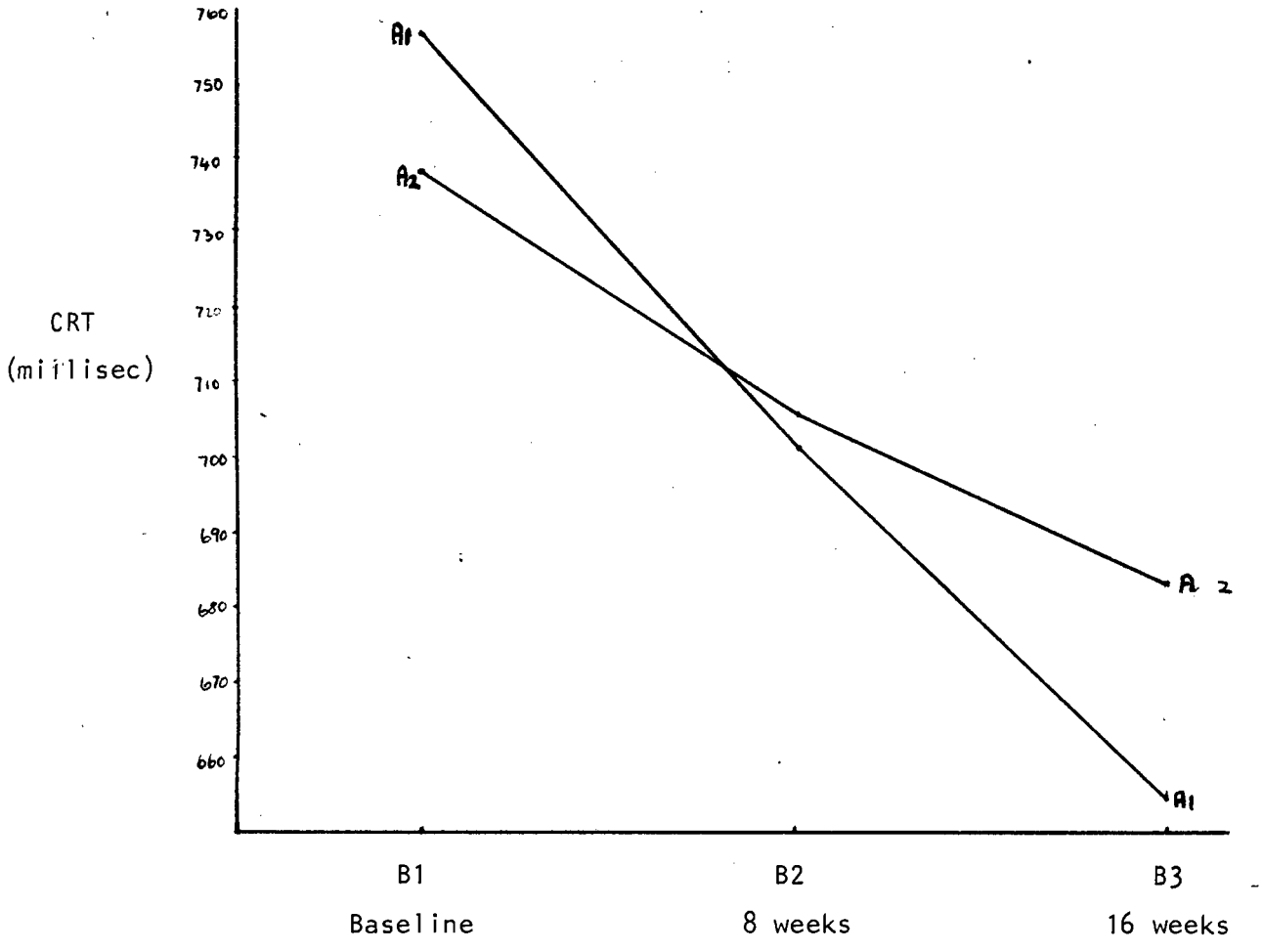


FIGURE 6: Choice Reaction Time (Reversed Condition Yellow Stimuli) Cell Mean Profile.

TABLE 14 Anova Summary Table for CRT for Yellow Stimuli under Reversed Conditions

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	890,77	0,05
Subjects	46	19121,28	
Within subjects			
B. Time of assessment	2	73966,38	21,80 ($p < ,01$)
AB. Interaction	2	6647,64	1,95
Residual	92	3392,55	

TABLE 15 Tukey HSD Results for CRT Overall Means for Yellow Stimuli under Reversed Conditions at each Assessment

	After 8 weeks	After 16 weeks
Baseline (B1)	5,21 ($p < ,01$)	9,35 ($p < ,01$)
After 8 weeks (B2)		4,14 ($p < ,01$)

5.2.2.5 Mean CRT Scores Under Standard Conditions: Red and Green Stimuli Together

TABLE 16 Mean CRT for Red and Green Stimuli under Standard Conditions

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	712,96 (125,09)	697,42 (116,15)	651,96 (84,60)
Sequence 2 (A2)	675,36 (106,93)	685,55 (104,17)	641,00 (94,07)

Mean scores of the two treatment groups at the three times of assessment are recorded in Table 16 and the cell mean profile illustrated in Figure 7. The cell mean profile shows slightly different directions of trends in the first trial period, but parallel trends of improvement in the second trial period. The statistical evaluation of these trends is shown in Table 17.

The effect of times of assessment alone is significant ($p < ,05$) and requires further analysis by means of Tukey HSD comparisons to determine the structure of the underlying variation. The results of Tukey HSD comparisons are presented in Table 18. The mean score at baseline is not significantly different from the mean score after 8 weeks, but is significantly poorer than that after 16 weeks ($p < ,05$). The difference between mean values after 8 weeks and after 16 weeks is also significant ($p < ,05$).

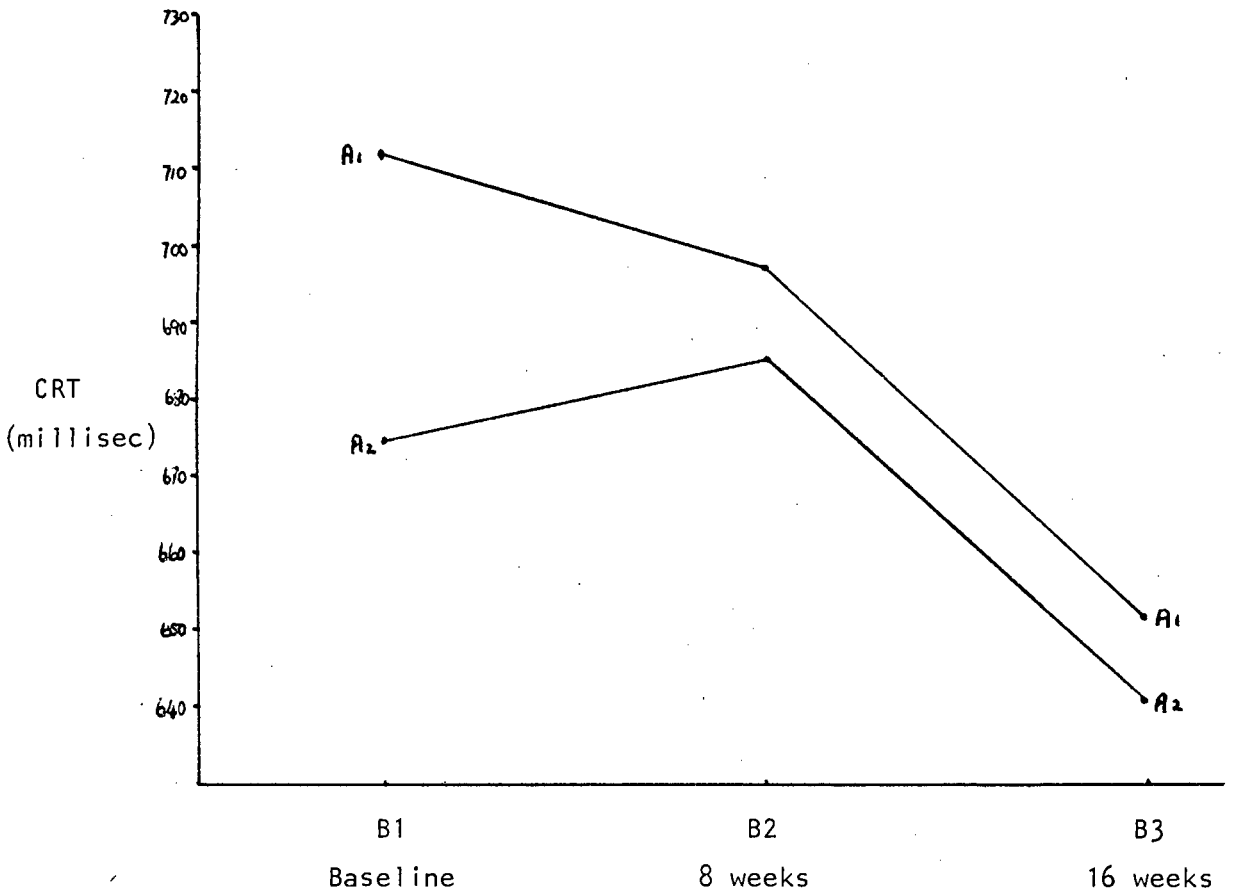


FIGURE 7: Choice Reaction Time (Standard Condition Red And Green Lights) Cell Mean Profile.

TABLE 17 Anova Summary Table for CRT for Red and Green Stimuli under Standard Conditions

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	14509,29	0,98
Subjects	46	14804,07	
Within subjects			
B. Time of assessment	2	34209,40	3,58 ($p < ,05$)
AB. Interaction	2	2724,82	0,28
Residual	92	9567,71	

TABLE 18 Tukey HSD Results for CRT Overall Means for Red and Green Stimuli under Standard Conditions at each Assessment

	After 8 weeks	After 16 weeks
Baseline (A1)	0,19	3,38 ($p < ,05$)
After 8 weeks		3,19 ($p < ,05$)

5.2.2.6 Mean CRT Scores Under Reversed Conditions: Red and Green Stimuli Together

TABLE 19 Mean CRT for Red and Green Stimuli under Reversed Conditions (milliseconds)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	830,92 (160,39)	789,27 (129,23)	757,85 (98,93)
Sequence 2 (A2)	832,32 (162,33)	755,18 (100,99)	767,77 (105,24)

Mean CRT values for each group at the three times of assessment are recorded in Table 19, and illustrated in Figure 8. The cell mean profile shows sharp drops in CRT scores in both groups in the first trial period, but differing trends in the second trial period, the decline in scores not being continued in the Sequence 2 subjects. The analysis of these trends is reported in Table 20.

The only effect to emerge significant is the B main effect, the trials effect which is highly significant ($p < ,01$). Further analysis using Tukey HSD comparisons is required to investigate the underlying trends in this factor.

The results of Tukey HSD comparisons are presented in Table 21. The differences between baseline scores and scores after 8 and 16 weeks are both significant ($p < ,01$) but the difference between scores

after 8 weeks and those after 16 weeks is not significant.

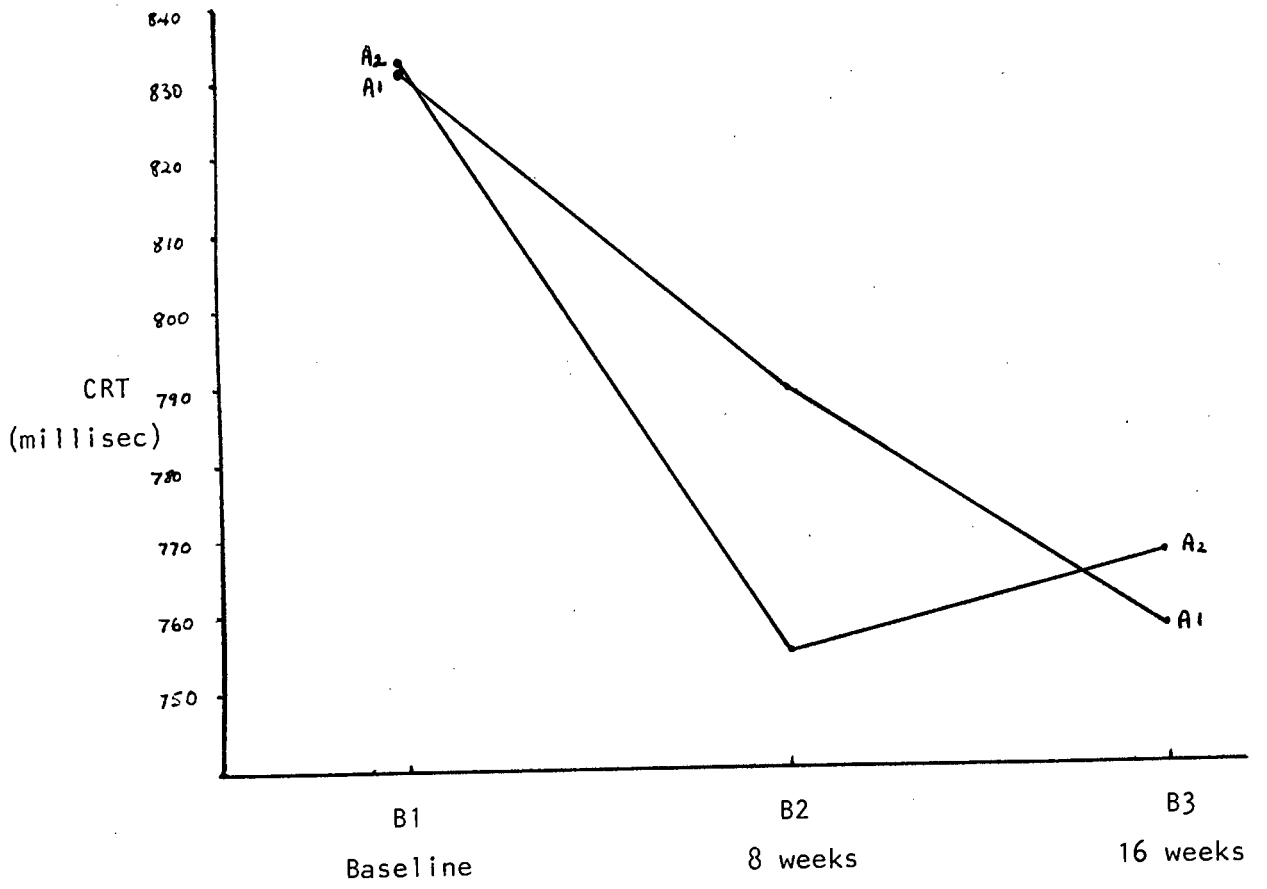


FIGURE 8: Choice Reaction Time (Reversed Condition Red And Green Lights) Cell Mean Profile.

TABLE 20 Anova Summary Table for CRT for Red and Green Stimuli under Reversed Conditions

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	2060,09	0,05
Subjects	46	38864,04	
Within subjects			
B. Time of assessment	2	66348,28	11,79 ($p < ,01$)
AB. Interaction	2	6491,98	1,15
Residual	92	5627,78	

TABLE 21 Tukey HSD Results for CRT Overall Means for Red and Green Stimuli under Reversed Conditions at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	5,48 ($p < ,01$)	6,35 ($p < ,01$)
After 8 weeks		0,87

5.2.3.1 Purdue Pegboard Test (PPT): Preferred Hand Task

The means of the two treatment groups at the three times of assessment for three trial total scores on the PPT - Preferred Hand Task are presented in Table 22 and illustrated in Figure 9. The cell mean profile shows similar moderate increases in both groups in the first trial period, followed by further moderate increases in the second trial period for the Sequence 2 group but a sharp decline is seen in the Sequence 1 group for this period. Table 23 presents the results of statistical analysis of these trends.

TABLE 22 Mean Purdue Pegboard Test Preferred Hand Task (PPT-PHT) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	42,31 (6,19)	43,27 (5,23)	41,85 (8,81)
Sequence 2 (A2)	42,23 (5,74)	43,68 (5,68)	44,68 (5,84)

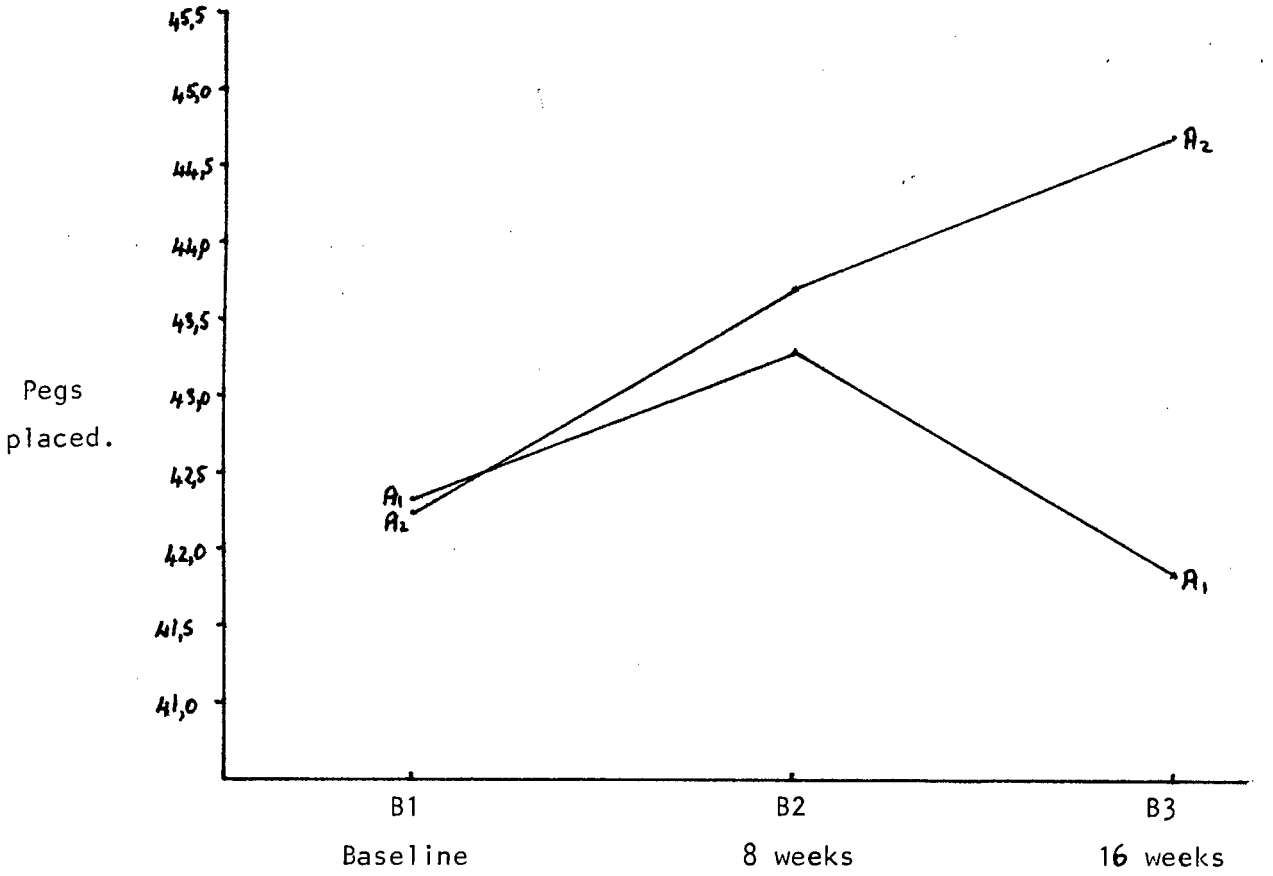


FIGURE 9: Purdue Pegboard Test Preferred Hand Task Cell Mean Profile.

TABLE 23 Anova Summary Table for PPT - Preferred Hand Task Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	39,87	0,52
Subjects	46	76,67	
Within subjects			
B. Time of assessment	2	19,84	0,86
AB. Interaction	2	29,03	1,25
Residual	92	23,18	

The results presented in Table 23 indicate no significant trends in the data. However the assumption of homogeneity of residual variance is violated (F max = 6,32; df = 2 and 44; $p < ,01$). As this might imply that a real interaction might be obscured, it is necessary to calculate Simple Main Effects. These results are presented in Table 24.

TABLE 24 Simple Main Effects Summary Table for PPT-Preferred Hand Task Scores

Source	df	MS	F Ratio
A at B_1	1	0,00	0,00
A at B_2	1	2,00	0,05
A at B_3	1	95,43	2,32
Within	138	41,07	
B at A_1	2	13,65	0,59
B at A_2	2	33,33	1,44
Residual	92	23,18	

None of the SMEs attain statistical significance and it can be concluded that the violation of homogeneity of variance has not obscured any effects. There is no systematic variation in this data related to either independent variable nor to interaction effects.

5.2.3.2 Purdue Pegboard Test (PPT): Non-Preferred Hand Task

Mean three trial total scores for PPT-Non-Preferred Hand performance for the two treatment groups at the three times of assessment are presented in Table 25 and illustrated in Figure 10. The cell mean profile indicates slight increases throughout the full trial period for both groups.

TABLE 25 Mean PPT Non-Preferred Hand Task (PPT-NPHT) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	40,15 (6,74)	41,12 (4,96)	42,04 (4,77)
Sequence 2 (A2)	41,59 (4,06)	42,27 (4,37)	42,64 (4,40)

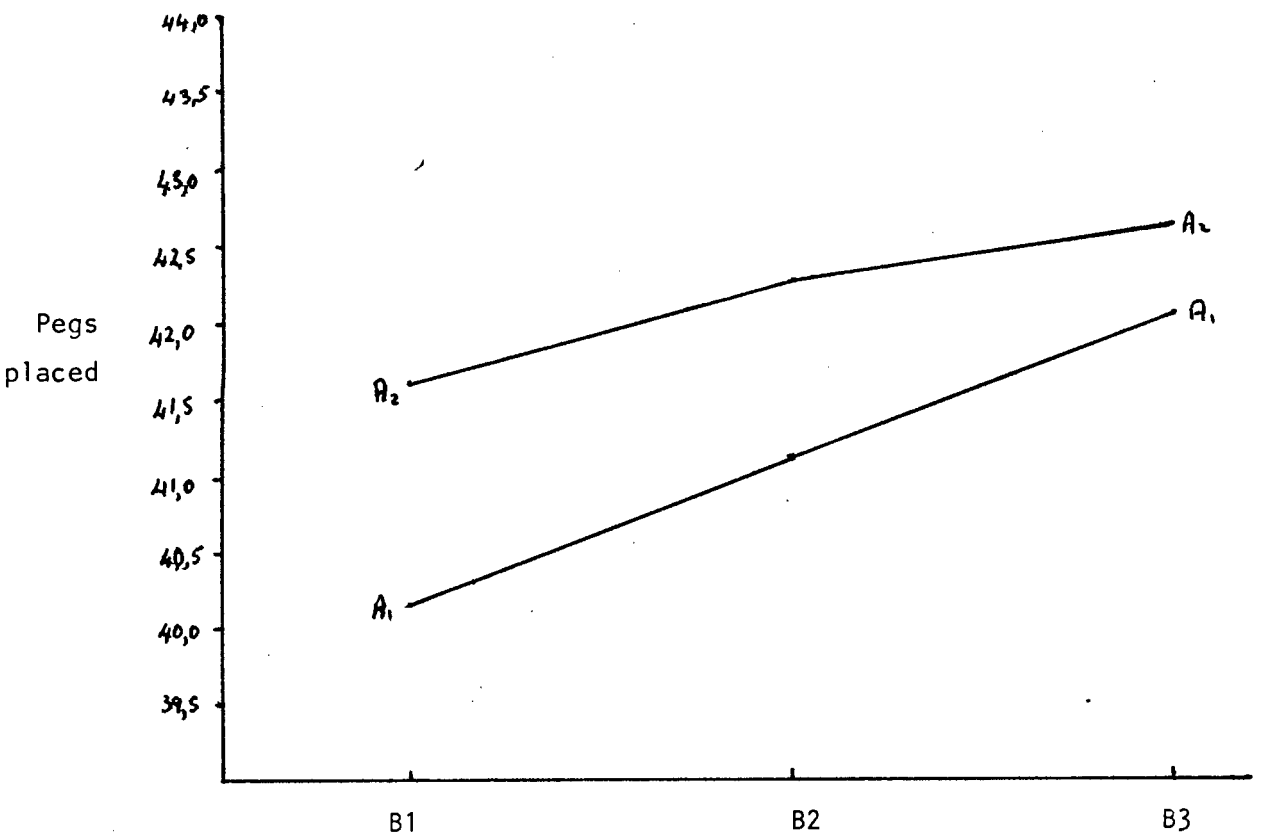


FIGURE 10: Purdue Pegboard Test Non-Preferred Hand Task Cell Mean Profile.

TABLE 26 Anova Summary Table for PPT - Non-Preferred Hand Task

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	40,48	0,64
Subjects	46	63,43	
Within subjects			
B. Time of assessment	2	25,71	4,27 ($p < ,05$)
AB. Interaction	2	2,17	0,36
Residual	92	6,02	

Results of statistical analysis yield only a significant trials effect ($p < ,05$). This requires further analysis to determine the structure of differences underlying it by means of Tukey HSD comparisons. These results are presented in Table 27.

Table 27 Tukey HSD Results for PPT-NPHT Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-2,37	-5,06 ($p < ,05$)
After 8 weeks		-1,83

Analysis of the significant B effect yields only one significant comparison between scores at baseline and after 16 weeks ($p < ,05$), this being a cumulative total of two smaller non-significant increases over time.

5.2.3.3 Purdue Pegboard Test (PPT): Simultaneous Hands Task

Mean three trial total scores for PPT-Simultaneous Hands performance

for the two treatment groups at the three times of assessment are presented in Table 28 and illustrated in Figure 11. The cell mean profile reveals different trends for the two treatment groups with Sequence 2 subjects consistently achieving higher scores. The results of statistical analysis of these trends are presented in Table 29.

TABLE 28 Mean PPT - Simultaneous Hands Task (PPT-SHT) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	33,04 (5,46)	32,56 (5,35)	33,12 (5,14)
Sequence 2 (A2)	33,59 (4,52)	34,32 (5,07)	34,32 (4,03)

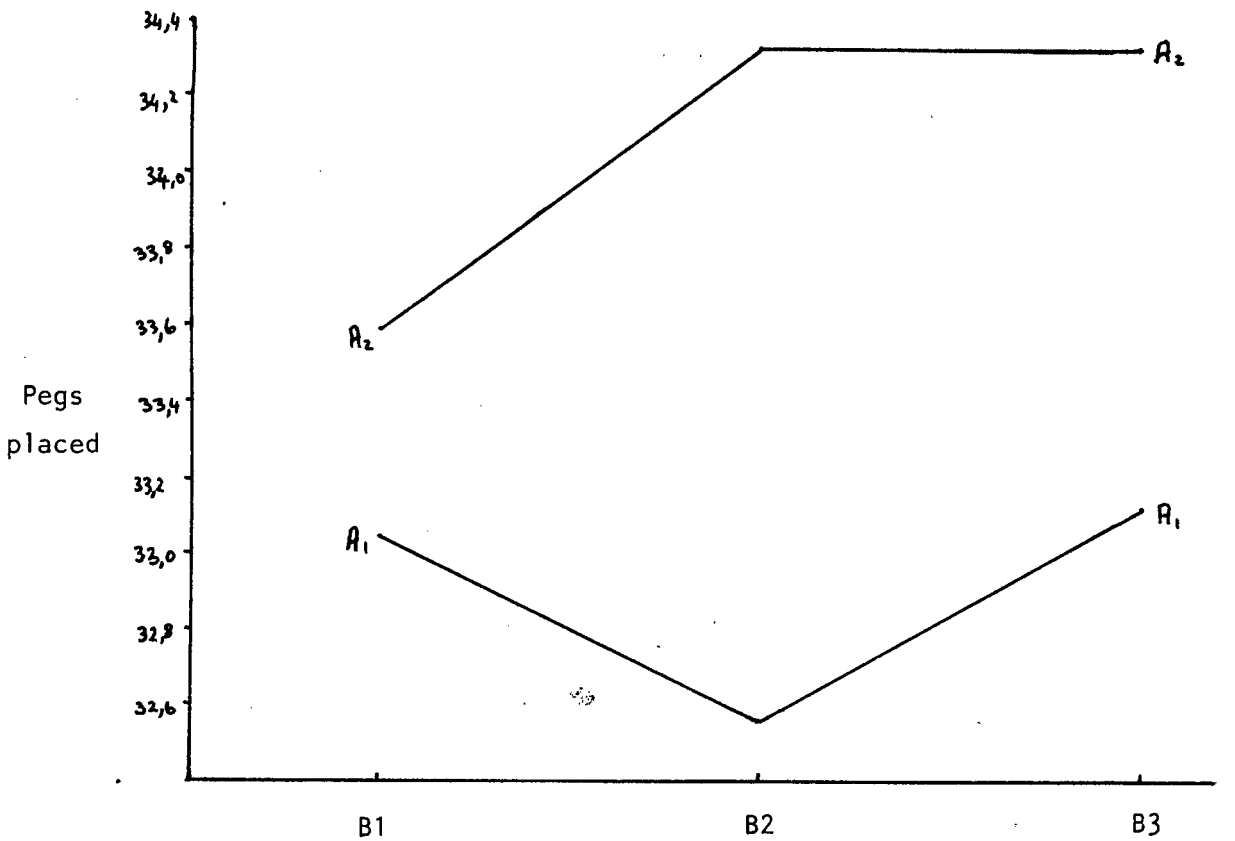


FIGURE 11: Purdue Pegboard Test Simultaneous Hands Task Cell Mean Profile.

TABLE 29 Anova Summary Table for PPT-Simultaneous Hands Task

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	47,99	0,73
Subjects	45	65,90	
Within subjects			
B. Time of assessment	2	2,00	0,48
AB. Interaction	2	4,27	1,01
Residual	90	4,21	

Analysis reveals no significant relationships between variables on this subtest. No further analysis may be attempted.

5.2.4 Wechsler Adult Intelligence Scale Subtests

All scores usedin these analyses are untransformed raw scores.

5.2.4.1 Information Subtest

Mean Information subtest raw scores for the two treatment groups at the three times of assessment are presented in Table 30, and illustrated in Figure 12. The trends shown by the cell mean profile reveal parallel marginal increases in scores throughout the trial period in the groups. The results of statistical analysis of these scores are presented in Table 31.

TABLE 30 Mean WAIS Information Subtest Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	16,69 (3,74)	17,19 (3,49)	17,62 (2,98)
Sequence 2 (A2)	15,55 (3,83)	15,86 (3,88)	16,23 (3,88)

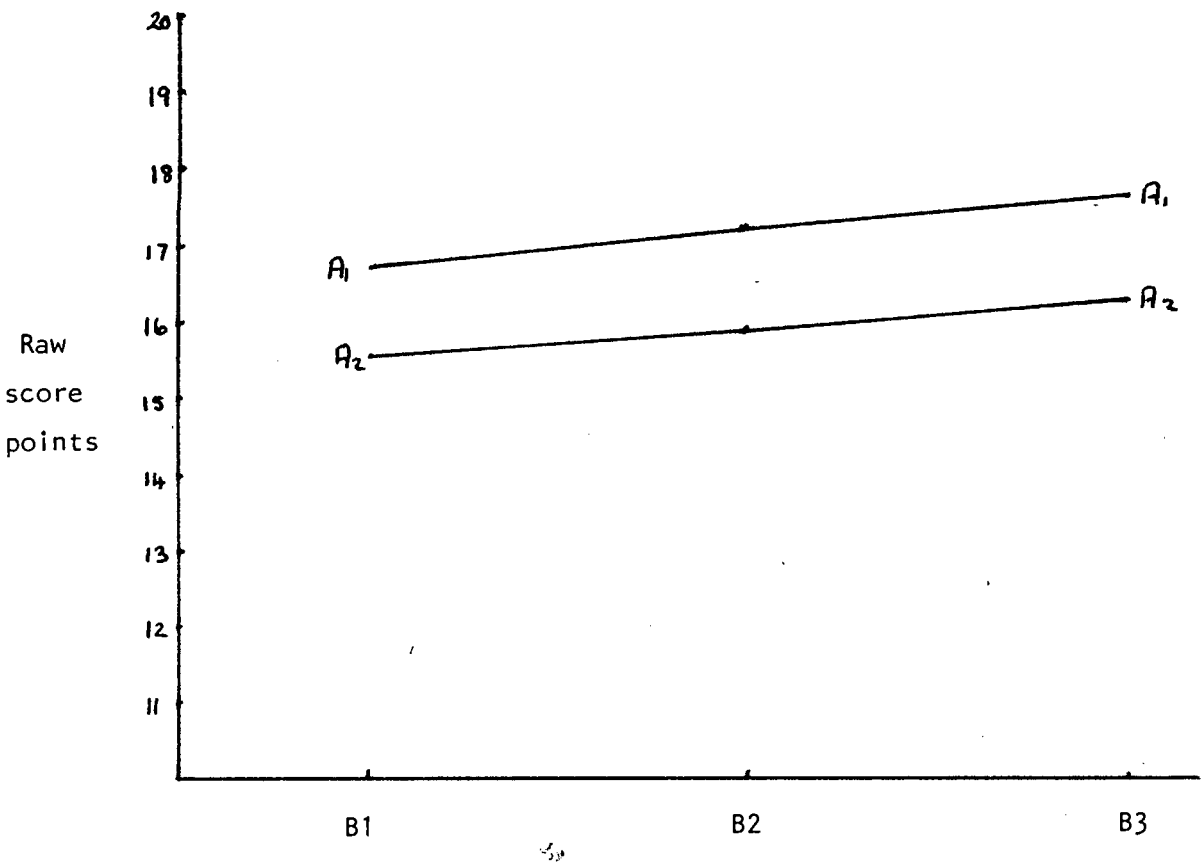


FIGURE 12: WAIS Information Subtest Cell Mean Profile.

TABLE 31 Anova Summary Table for WAIS Information Subtest

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	59,30	1,63
Subjects	46	36,39	
Within subjects			
B. Time of assessment	2	7,67	4,98 ($p < ,01$)
AB. Interaction	2	0,19	0,12
Residual	92	1,54	

The results shown in Table 31 indicate no interaction or A (treatment sequence) effects, but a highly significant B (trials effect ($p <,01$) which requires further analysis by means of Tukey HSD comparisons. These statistical results are presented in Table 32.

TABLE 32 Tukey HSD Results for Information Subtest Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-2,28	-4,50 ($p <,01$)
After 8 weeks		-2,22

Only one Tukey HSD comparison is statistically significant. This is the comparison between scores at baseline and after 16 weeks ($p <,01$) which reflects the cumulative effects of consistent smaller though non-significant increases in trial periods one and two, as seen in Figure 12.

5.2.4.2 Digit Span Subtest

Mean Digit Span raw scores for the two treatment groups at the three

times of assessment are presented in Table 33 and illustrated in Figure 13. The cell mean profile reveals parallel slightly increasing scores throughout the trial. The differences between the treatment groups at all times of assessment are extremely small. Results of statistical analysis of the data are presented in Table 34.

TABLE 33 Mean WAIS Digit Span Subtest Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	10,88 (2,16)	11,38 (2,47)	11,42 (2,34)
Sequence 2 (A2)	11,00 (1,90)	11,55 (2,04)	11,64 (2,34)

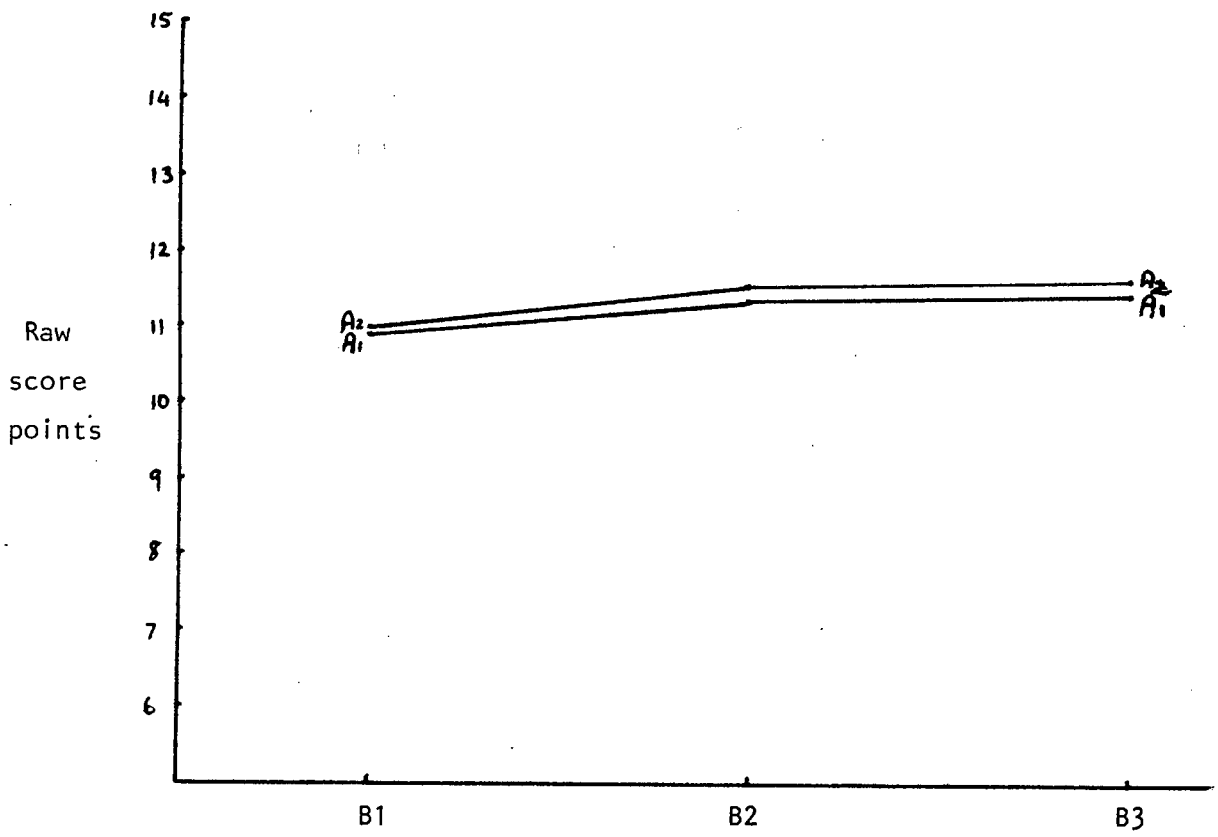


FIGURE 13: WAIS Digit Span Subtest Cell Mean Profile.

TABLE 34 Anova Summary Table for Digit Span Subtest

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,95	0,08
Subjects	46	12,24	
Within subjects			
B. Time of assessment	2	4,95	3,77 ($p < ,05$)
AB. Interaction	2	0,03	0,02
Residual	92	1,31	

Statistical analysis of Digit Span subtest data only reveals a significant B (trials) effect ($p < ,05$) which requires further analysis be means of Tukey HSD comparisons. These results are presented in Table 35. The sole significant difference underlying the significant effect of time of assessment is the difference between scores at baseline and those after 16 weeks ($p < ,05$). This reflects accumulated consistent, smaller and non-significant score increases in trial periods one and two.

TABLE 35 Tukey HSD Results for Digit Span Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-3,06	-3,41 ($p < ,05$)
After 8 weeks		-0,35

5.2.4.2a Digit Span: Digits Forwards Only

Mean raw scores for the two treatment groups at the three times of assessment for the Digits Forward section of Digit Span are presented

in Table 36 and illustrated in Figure 14. The cell mean profile reveals very similar, minimal changes in scores during the trial period. Slight increases are seen in all cases except that a slight decrease in scores is seen for Sequence 2 subjects in the second trial period. Results of analysis of the data are presented in Table 37.

TABLE 36 Mean Digits Forwards Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	6,15 (1,56)	6,42 (1,30)	6,50 (1,14)
Sequence 2 (A2)	6,18 (1,22)	6,55 (1,22)	6,41 (1,37)

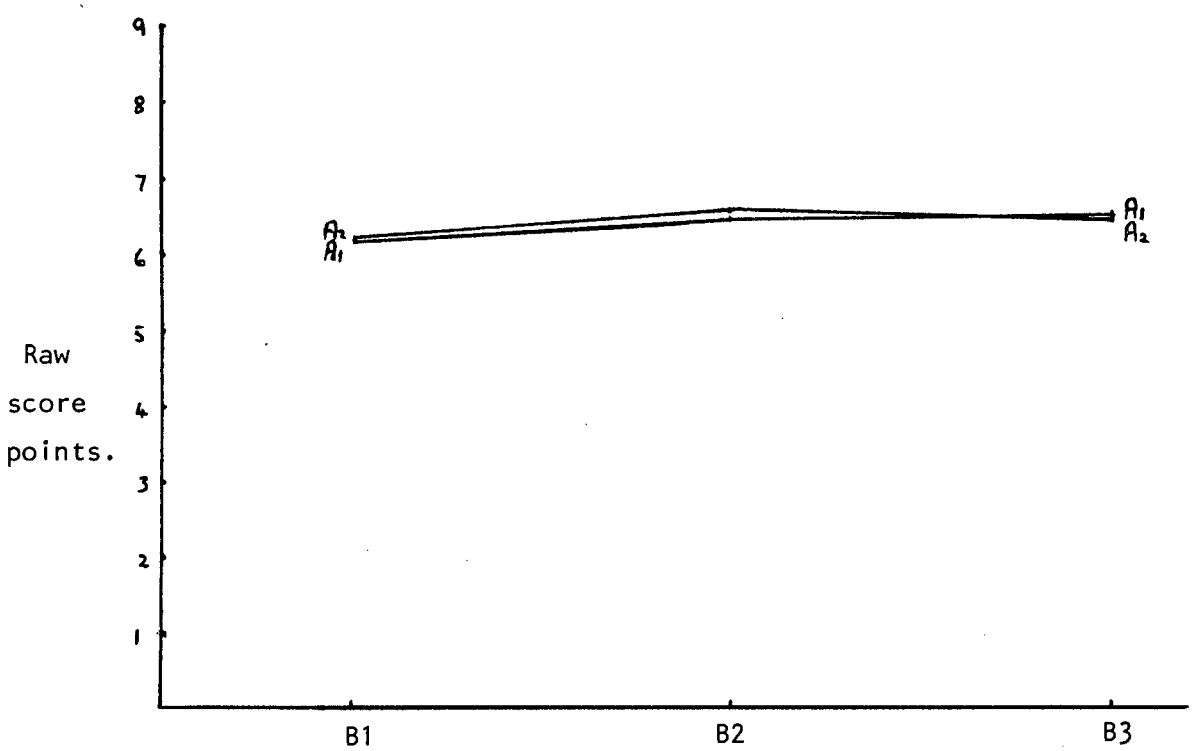


FIGURE 14: WAIS Digits Forwards Cell Mean Profile.

TABLE 37 Anova Summary Table for Digits Forwards Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,01	0,00
Subjects	46	3,03	
Within subjects			
B. Time of assessment	2	1,46	1,89
AB. Interaction	2	0,14	0,18
Residual	92	0,77	

The anova summary table reveals no significant effects operating on Digits Forwards scores. No further analysis is possible.

5.2.4.2.b Digit Span: Digits Backwards Only

Mean raw scores for the two treatment groups at the three times of assessment for the Digits backwards section of Digit Span are presented in Table 38 and illustrated in Figure 15.

TABLE 38 Mean Digits Backwards Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	4,73 (1,48)	4,96 (1,68)	4,92 (1,60)
Sequence 2 (A2)	4,82 (1,18)	5,00 (1,27)	5,23 (1,31)

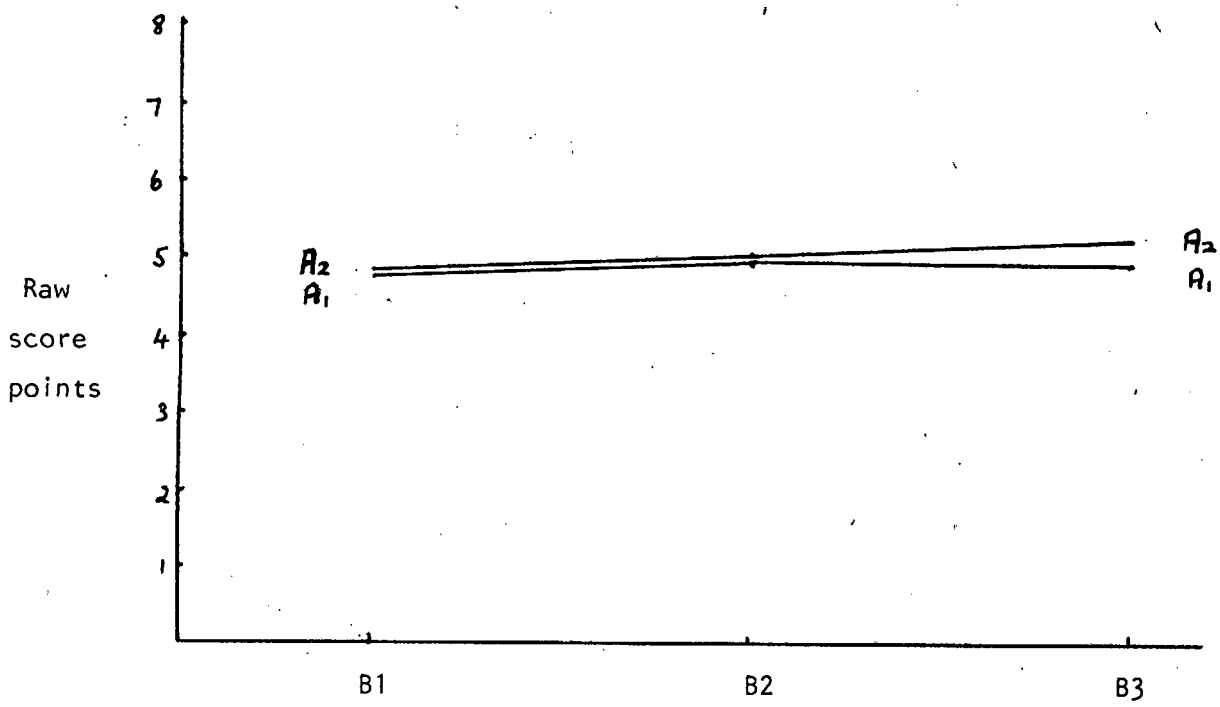


FIGURE 15: WAIS Digits Backwards Cell Mean Profile.

It can be seen from Figure 15 that the trends for the two treatment groups are almost parallel in both trial periods. Except for Sequence 1 subjects in the second trial period, all score changes are increases. Results of statistical analysis of the data are presented in Table 39.

TABLE 39 Anova Summary Table for Digits Backwards Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,73	0,14
Subjects	46	5,30	
Within subjects			
B. Time of assessment	2	1,13	2,29
AB. Interaction	2	0,24	0,48
Residual	92	0,49	

Statistical analysis reveals no significant effects operating on Digits Backwards scores. No further analysis is possible.

5.2.4.3 Similarities Subtest

Mean scores for the two treatment groups at the three times of assessment on the Similarities subtest are presented in Table 40 and illustrated in Figure 16. The cell mean profile reveals similar changes in scores, with the differences between treatment groups being very small at all times of assessment. Scores tend to increase till 8 weeks but to decline after 16 weeks. Results of statistical analysis of these scores are presented in Table 41.

TABLE 40 Mean WAIS Similarities Subtest Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	15,85 (4,09)	16,58 (3,67)	16,54 (3,60)
Sequence 2 (A2)	15,68 (3,63)	16,55 (3,89)	16,41 (3,61)

TABLE 41 Anova Summary Table for Similarities Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,42	0,01
Subjects	46	37,26	
Within subjects			
B. Time of assessment	2	9,11	3,62 ($p < ,05$)
AB. Interaction	2	0,06	0,02
Residual	92	2,52	

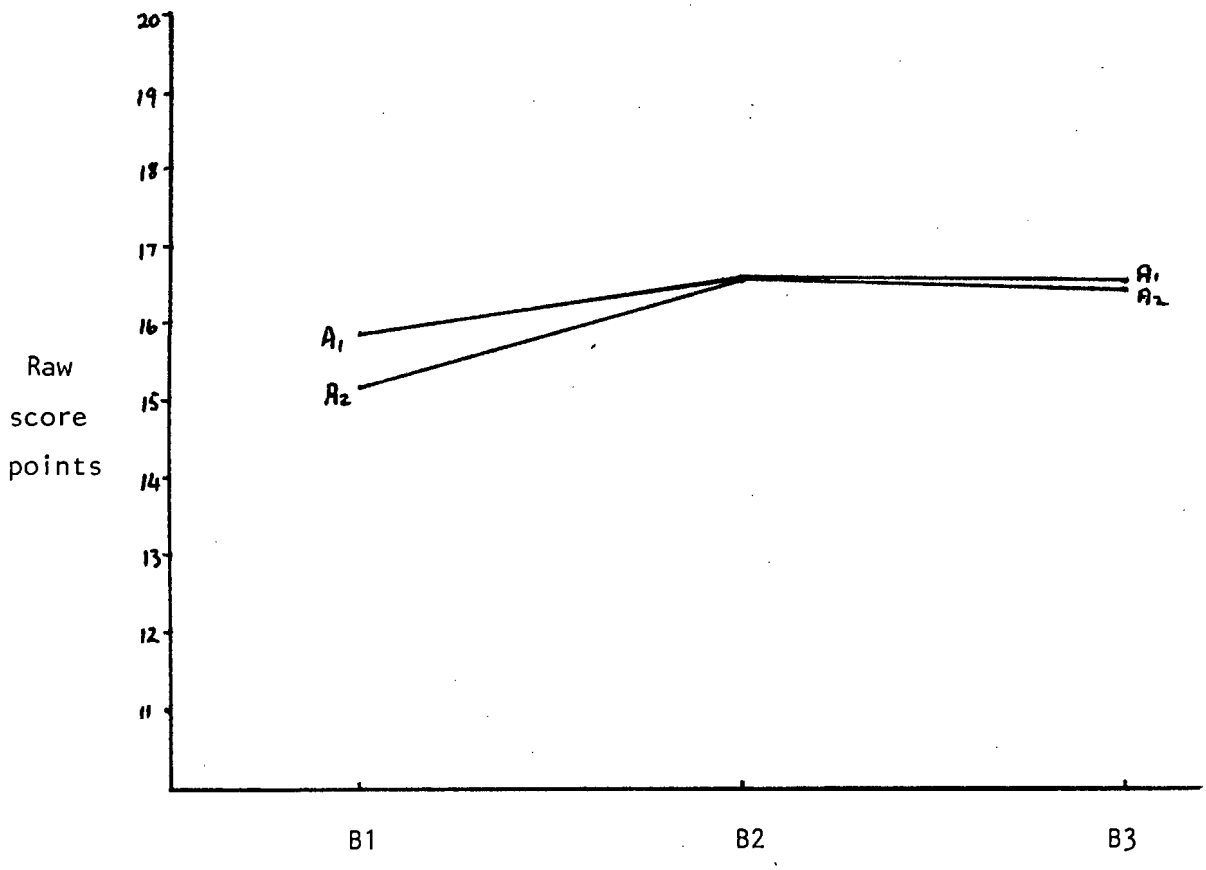


FIGURE 16: WAIS Similarities Subtest Cell Mean Profile.

Table 41 reveals only one significant effect operating on Similarities This is the trials effect ($p < ,05$), which requires further analysis by means of Tukeys HSD comparisons to determine the underlying structure of differences. The results of these comparisons are presented in Table 42.

TABLE 42 Tukey HSD Results for Similarities Subtest Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-3,48 ($p < ,05$)	-3,09
After 8 weeks		0,39

From Table 42, it can be seen that the significant effect of time of assessment reflects only the improvement of scores between baseline and those obtained after 8 weeks ($p < ,05$).

5.2.4.4 Object Assembly Subtest

Mean raw scores for the two treatment groups at the three times of assessment on the Object Assembly subtest are presented in Table 43 and illustrated in Figure 17. The cell mean profile reveals parallel increases in both treatment groups throughout the trial, more marked in the first trial period.

TABLE 43 Mean WAIS Object Assembly Subtest Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	14,81 (3,64)	17,54 (3,91)	18,62 (3,24)
Sequence 2 (A2)	16,32 (3,58)	18,41 (2,94)	19,45 (3,05)

Results of statistical analysis of Object Assembly scores are presented in Table 44. The sole significant result is a highly significant trials effect ($p < ,01$). This requires further analysis by means of Tukey HSD comparisons to determine the structure of underlying differences.

TABLE 44 Anova Summary Table for Object Assembly Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	41,19	1,55
Subjects	46	26,62	
Within subjects			
B. Time of assessment	2	150,89	34,92 ($p < ,01$)
AB. Interaction	2	1,71	0,40
Residual	92	4,32	

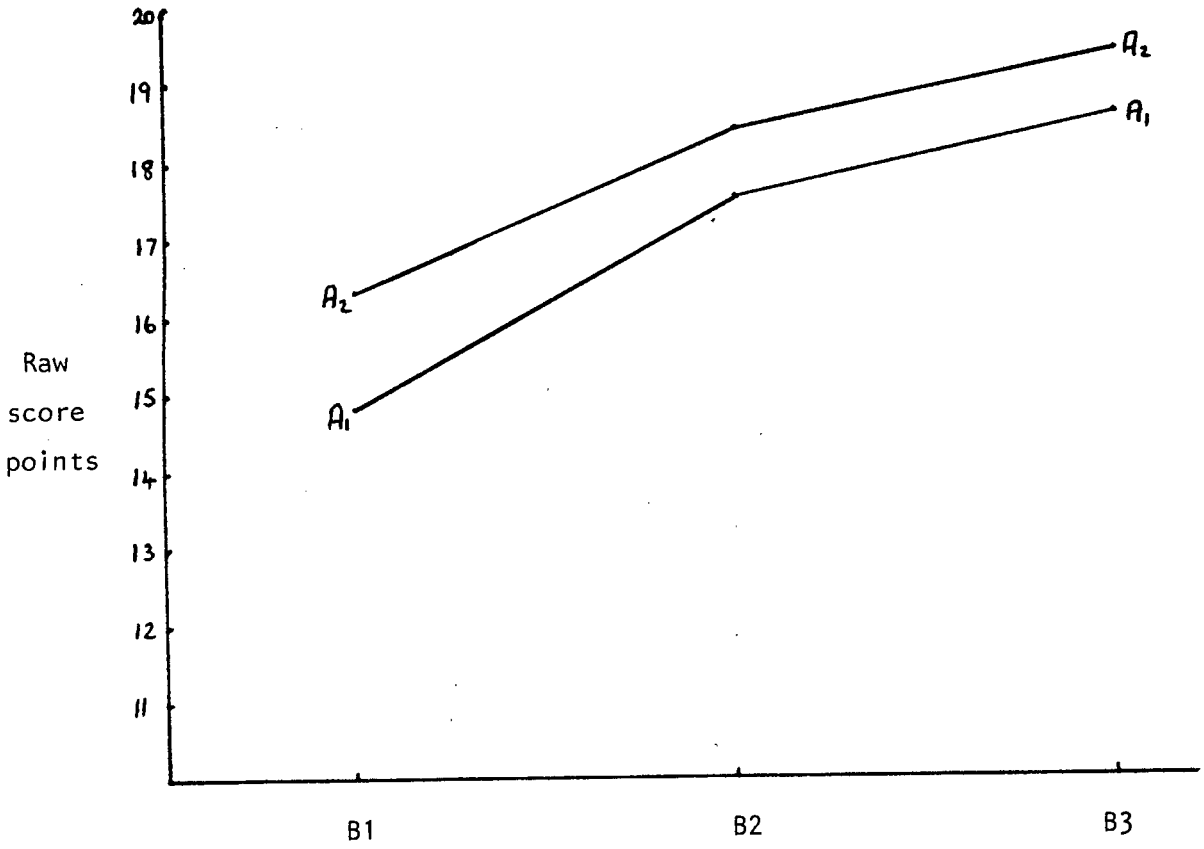


FIGURE 17: WAIS Object Assembly Subtest Cell Mean Profile.

TABLE 45 Tukey HSD Results for Object Assembly Subtest Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-8,03 ($p < ,01$)	-11,57 ($p < ,01$)
After 8 weeks		- 3,53 ($p < ,05$)

Results of Tukey HSD comparisons are presented in Table 45. All comparisons yield significant differences reflecting significant increases in scores in both trial periods. The increase is greater in the first trial period ($p < ,01$).

5.2.4.5 Block Design Subtest

Mean Block Design scores for the two treatment groups at the three times of assessment are presented in Table 46 and illustrated in Figure 18. Inspection of the cell mean profile reveals a large difference between groups at baseline, and differing trends for the two treatment groups. Sequence 1 subjects' scores improve markedly in the first trial period but decline slightly in the second, while Sequence 2 subjects' scores remain approximately constant over the first trial period but improve substantially over the second trial period. At no time of assessment are scores of the treatment groups similar.

Results of the statistical analysis of the Block Design scores are presented in Table 47.

TABLE 46 Mean WAIS Block Design Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	20,19 (6,82)	22,35 (6,62)	22,00 (6,09)
Sequence 2 (A2)	24,55 (5,66)	24,5 (6,08)	26,68 (5,73)

TABLE 47 Anova Summary Table for Block Design Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	497,28	4,64 ($p < ,05$)
Subjects	46	107,19	
Within subjects			
B. Time of assessment	2	46,42	10,82 ($p < ,01$)
AB. Interaction	2	22,51	5,25 ($p < ,01$)
Residual	92	4,29	

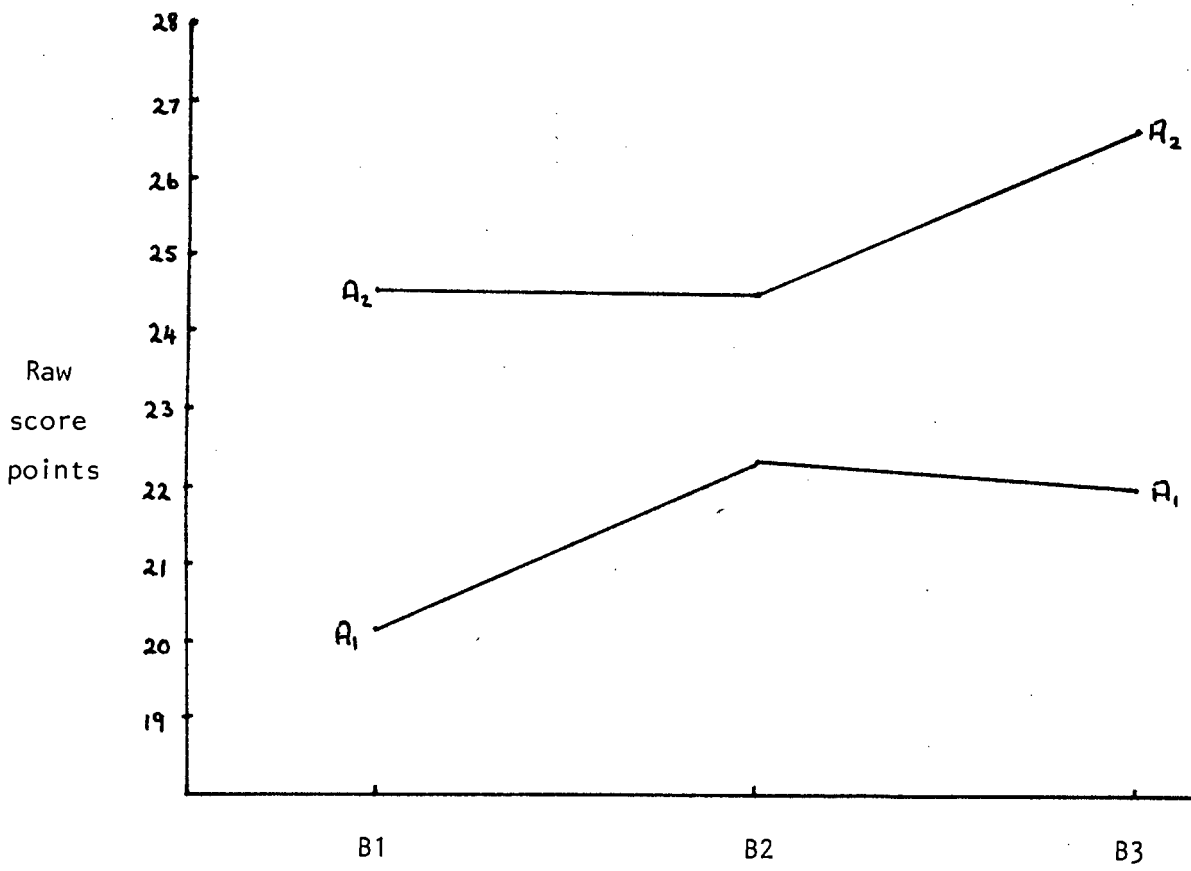


FIGURE 18: WAIS Block Design Subtest Cell Mean Profile.

Results of statistical analysis of Block Design scores, as presented in Table 47, indicate significant interaction ($p < ,01$) and treatment main effects. The interaction requires further analysis by means of calculation of simple main effects. These are presented in Table 48.

TABLE 48 Simple Main Effects Summary Table for Block Design Subtest Scores

Source	df	MS	F ratio
A at B_1	1	222,33	5,76 ($p < ,05$)
A at B_2	1	55,52	1,44
A at B_3	1	260,94	6,76 ($p < ,05$)
Within	138	38,59	
B at A_1	2	34,97	8,15 ($p < ,01$)
B at A_2	2	34,10	7,95 ($p < ,01$)
Residual	92	4,29	

The analysis of simple main effects yields significant results for the effect of treatments, at baseline and after 16 weeks (both $p < ,05$), but not after 8 weeks, and for the trials effect for each treatment group (both $p < ,01$).

The results of inter-cell comparisons to determine the structures of scores underlying these results, and to assess their degree of significance, are presented in Table 49 for the effects of treatment on time of assessment, and in Table 50 and Table 51, for the effects of time of assessment on treatments.

TABLE 49 Tukey HSD Results for the Effects of Treatments on Block Design Subtest Scores at Specific Assessments (two levels only).

Source	Tukey value	df	Level of Significance
A at B_1 (Difference at baseline)	-10,38	2;92	$p < ,01$
A at B_3 (Difference after 16 weeks)	-11,14	2;92	$p < ,01$

TABLE 50 Tukey HSD Results for Effects of Treatments on Block Design Subtest Scores within Group 1 (piracetam-placebo order)

	After 8 weeks	After 16 weeks
Baseline	-5,26 ($p < ,01$)	-4,42 ($p < ,01$)
After 8 weeks		0,85

TABLE 51 Tukey HSD Results for Effects of Treatments on Block Design Subtest Scores within Group 2 (placebo-piracetam order)

	After 8 weeks	After 16 weeks
Baseline	0,11	-4,84 ($p < ,01$)
After 8 weeks		-4,96 ($p < ,01$)

The effect of treatments at baseline and after 16 weeks only involve two levels in each case. The effect at baseline is highly significant ($p < ,01$) and indicates scores of Sequence 2 subjects are significantly higher than those of Sequence 1 subjects. The effect after 16 weeks is also highly significant ($p < ,01$) and also indicates scores in Sequence 2 subjects are significantly higher than those of Sequence 1 subjects.

The significant effect of time of assessment in Sequence 1 is based on significant differences between scores at baseline and the scores after 8 and 16 weeks (both $p < ,01$) but the difference between scores after 8 and 16 weeks is not significant. Both significant differences reflect increases over baseline scores, though the trend was partially reversed in the second trial period.

The significant effect of time of assessment in Sequence 2 is based on a significant increase in scores after 16 weeks relative to scores at baseline and after 8 weeks (both $p < ,01$). Scores at baseline and after 8 weeks do not differ significantly.

5.2.4.6 Digit Symbol Substitution Test (DSST)

Mean DSST scores for the two treatment groups at the three times of assessment are presented in Table 52 and illustrated in Figure 19. The cell mean profile reveals similar increasing trends in the first trial period but this only continues in trial period two for the Sequence 2 subjects, while the trend for Sequence 1 subjects flattens off.

TABLE 52 Mean WAIS Digit Symbol Substitution Test (DSST) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	33,73 (9,84)	37,29 (9,76)	37,58 (10,24)
Sequence 2 (A2)	33,14 (8,66)	35,91 (9,48)	38,18 (9,97)

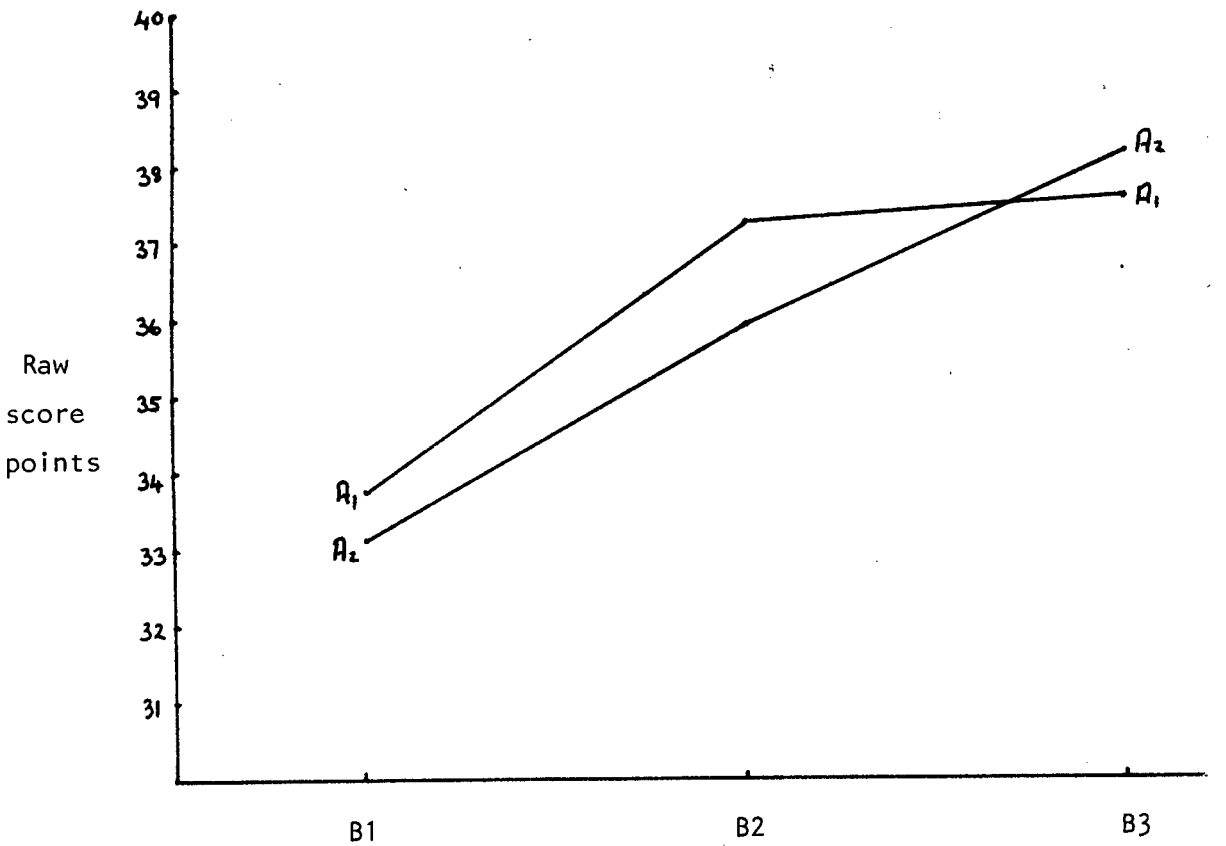


FIGURE 19: WAIS Digit Symbol Substitution Test Cell Mean Profile.

TABLE 53 Anova Summary Table for DSST Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	7,24	0,03
Subjects	46	261,65	
Within subjects			
B. Time of assessment	2	249,36	24,56 ($p < ,01$)
AB. Interaction	2	11,69	1,15
Residual	92	10,15	

Table 53 presents the results of statistical analysis of DSST scores. Only a significant trials effect emerges ($p < ,01$). This requires further analysis by means of Tukey HSD comparisons, the results of which are presented in Table 54.

TABLE 54 Tukey HSD Results for DSST Overall Means at each Assessment

	After 8 weeks	After 16 weeks
Baseline	-6,85 ($p < ,01$)	-9,65 ($p < ,01$)
After 8 weeks		-2,80

From Table 54 it emerges that the significant effect of time of assessment is due to significant increases over baseline scores after 8 weeks and after 16 weeks (both $p < ,01$). The change in scores between weeks 8 and 16 represents a further increase but this is not significant in itself.

5.2.4.7 Pro-Rated WAIS IQ (PIQ)

Mean PIQ scores for the two treatment groups at the three times of assessment are presented in Table 55 and illustrated in Figure 20. The cell mean profile reveals consistent score increases by Sequence 2 subjects throughout the trial, while Sequence 1 subjects show increases in scores in the first trial period but not in the second, where scores level off. The results of statistical analysis of the data are presented in Table 56.

TABLE 55 Mean Pro-Rated WAIS IQ (PIQ) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	103,58 (14,68)	110,69 (15,52)	110,96 (13,73)
Sequence 2 (A2)	106,05 (11,36)	111,23 (12,15)	114,73 (14,28)

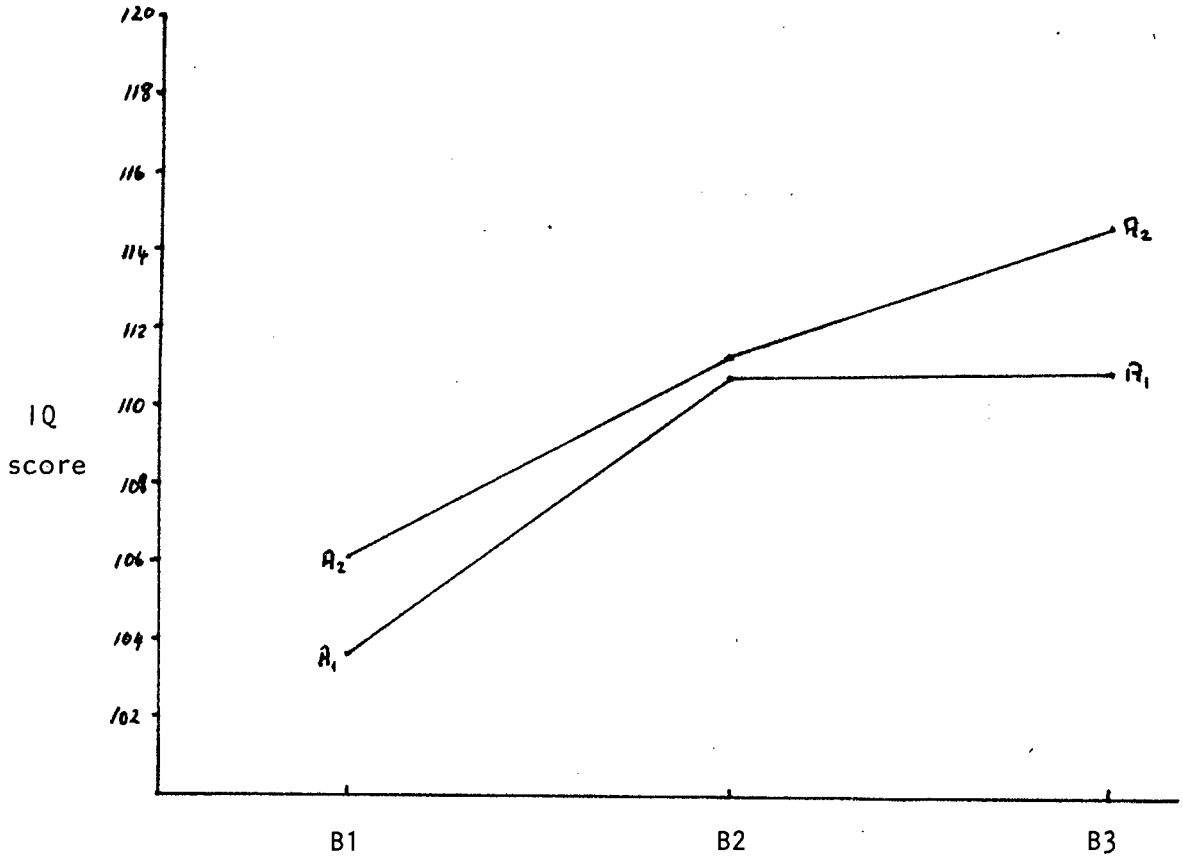


FIGURE 20: WAIS Pro-Rated IQ Cell Mean Profile.

TABLE 56 Anova Summary Table for PIQ Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	182,01	0,35
Subjects	46	526,35	
Within subjects			
B. Time of assessment	2	841,24	38,54 (p < ,01)
AB. Interaction	2	31,50	1,44
Residual	92	21,83	

Statistical analysis reveals only a significant trials effect ($p < ,01$). This requires further analysis by means of Tukey HSD comparisons to determine the structure of differences underlying this effect. Results of these comparisons are presented in Table 57.

TABLE 57 Tukey HSD Results for PIQ Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-9,16 ($p < ,01$)	-11,99 ($p < ,01$)
After 8 weeks		- 2,82

The results presented in Table 57 reveal that scores after 8 weeks and after 16 weeks both differ significantly from scores at baseline (both $p < ,01$), but do not differ significantly between themselves. The scores reflect a trend of increasing scores throughout the trial, with the major increase occurring in the first trial period.

5.2.5.1 Modified Card Soring Test (MCST): Total Presentations

Mean numbers of presentations for the two treatment groups at the three times of assessment are presented in Table 58 and illustrated in Figure 21. The cell mean profile reveals that the treatment groups differ at baseline and appear to follow differing trends thereafter. While Sequence 1 subjects require more presentations at baseline, but show progressively decreasing scores after 8 and 16 weeks, Sequence 2 subjects require fewer presentations at baseline, but show a slight increase in required presentations after 8 weeks. This is followed by a decrease after 16 weeks.

At no time do Sequence 1 subjects require as few presentations as the highest number required at any time by Sequence 2 subjects. Results of statistical analysis of this data are presented in Table 59.

TABLE 58 Mean Modified Card Sorting Test (MCST) Total Presentations

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	45,42 (4,37)	44,08 (4,75)	43,35 (4,24)
Sequence 2 (A2)	42,27 (4,99)	42,82 (4,93)	41,45 (4,45)

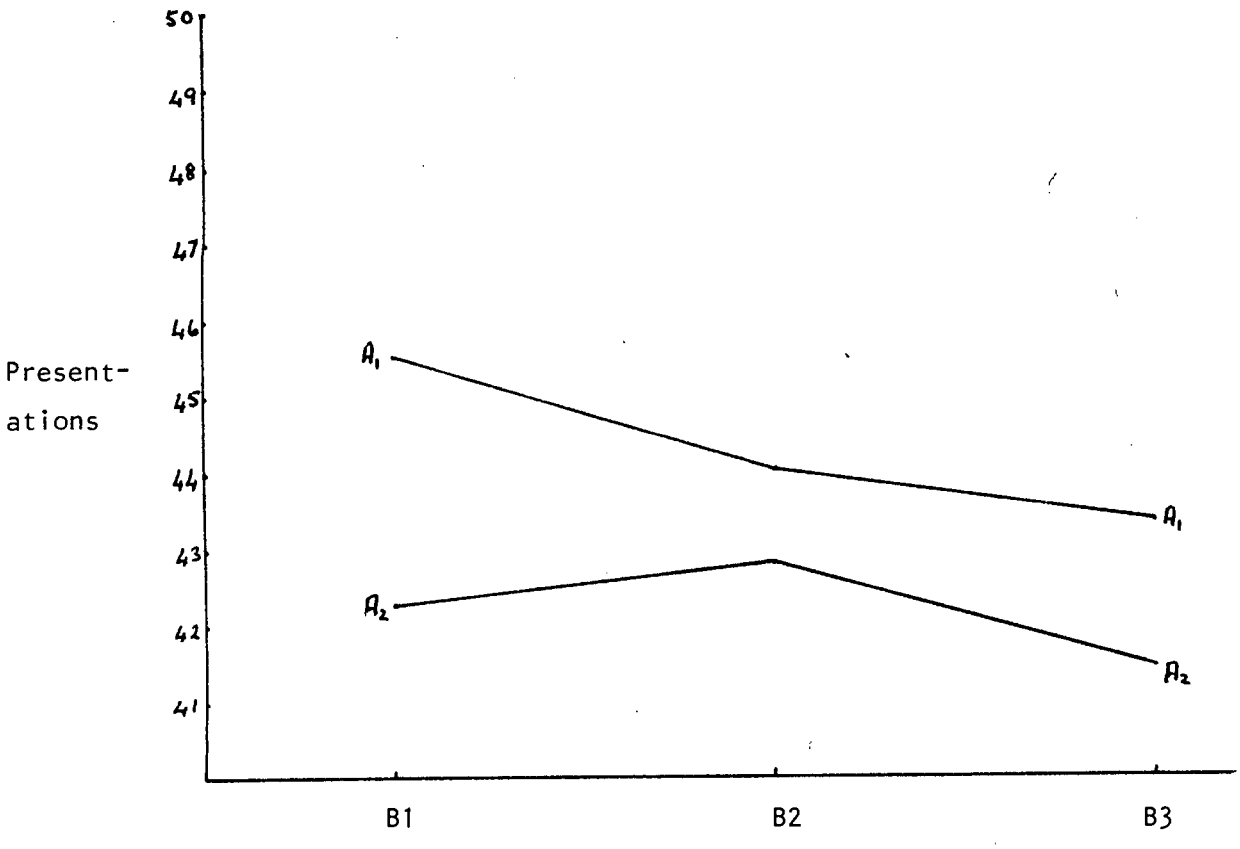


FIGURE 21: Modified Card Sorting Test - Total Presentations Cell Mean Profile.

TABLE 59 Anova Summary Table for MCST Total Presentations Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	157,70	3,57
Subjects	46	44,17	
Within subjects			
B. Time of assessment	2	26,64	2,69
AB. Interaction	2	11,05	1,18
Residual	92	9,89	

The results of statistical analysis presented in Table 59 indicate that there are no significant effects acting upon the number of presentations required to complete the MCST. There is a violation of homogeneity of residual error variance ($F_{max} = 2,51$; $df = 2$ and 44; $p < ,05$), but as no trends in Table 59 are significant, use of higher levels of significance does not change the conclusions drawn.

5.2.5.2 Modified Card Sorting Task (MCST): Sets Completed

Mean numbers of sets completed for each treatment group at each time of assessment are presented in Table 60 and illustrated in Figure 22. From the cell mean profile it can be seen that Sequence 2 subjects complete more sets at all times of assessment than do Sequence 1 subjects. In both treatment groups there is a continuing trend of slight increases throughout the trial. The results of statistical analysis of these data are presented in Table 61.

TABLE 60 Mean MCST Completed Sets

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	4,08 (1,94)	4,46 (1,98)	4,65 (2,02)
Sequence 2 (A2)	5,45 (1,34)	5,41 (1,01)	5,64 (1,14)

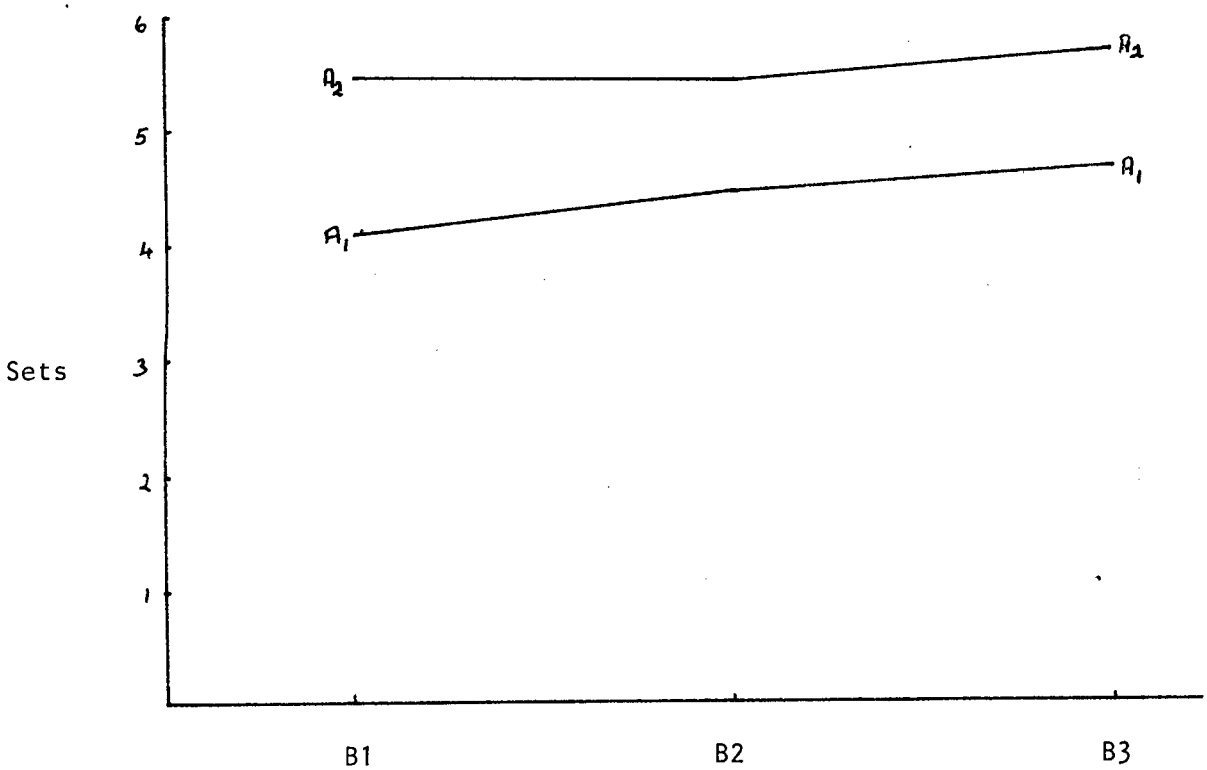


FIGURE 22: Modified Card Sorting Test - Completed Sets Cell Mean Profile.

TABLE 61 Anova Summary Table for MCST Sets Completed

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	43,46	6,11 ($p < ,05$)
Subjects	46	7,11	
Within subjects			
B. Time of assessment	2	1,72	3,00
AB. Interaction	2	0,68	1,18
Residual	92	0,57	

The results of statistical analysis, as presented in Table 61, indicate there is only one significant effect. This is the main effect of treatment sequence ($p < ,05$). For both subject variance and residual variance, the assumption of homogeneity of variance is violated (f max-subjects = 2,99; df = 2,22; $p < ,05$ and F max-residual = 2,33; df = 2,44; $p < ,05$). To compensate for this, a higher level of significance namely the ,01 level may be used. Using this level of significance, the treatment sequence effect does not attain significance, and it must be concluded that there are no effects systematically influencing the number of sets completed.

5.2.5.3 Modified Card Sorting Test (MCST): Total Error Scores

Mean MCST total error scores for the two treatment groups at the three times of assessment are presented in Table 62 and illustrated in Figure 23.

From Figure 23 it can be seen that the groups differ at baseline and the difference persists throughout the trial, though it narrows

TABLE 62 Mean MCST Total Error Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	14,65 (11,54)	11,77 (11,48)	9,19 (11,01)
Sequence 2 (A2)	7,36 (10,74)	5,36 (5,37)	4,32 (5,43)

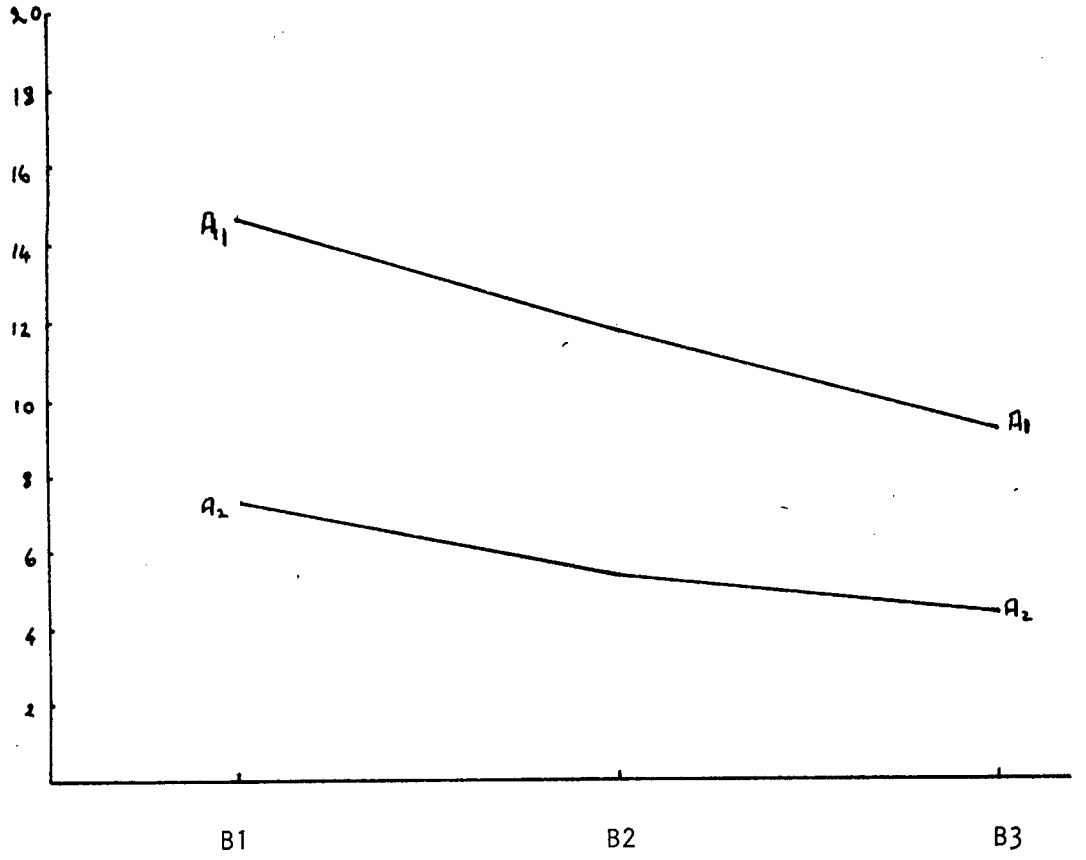


FIGURE 23: Modified Card Sorting Test - Total Errors Cell Mean Profile.

slightly after 16 weeks. Subjects in Sequence 1 make more errors than subjects in Sequence 2 at all times of assessment. Results of statistical analysis of these scores are presented in Table 63.

TABLE 63 Anova Summary Table for MCST Total Error Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	1369,79	5,82 ($p < ,05$)
Subjects	46	235,44	
Within subjects			
B. Time of assessment	2	217,18	8,11 ($p < ,01$)
AB. Interaction	2	17,81	0,67
Residual	92	26,77	

The results shown in Table 63 indicate significant effects due to treatment sequence and to time of assessment (trials). However, these findings are complicated for the effect of treatment sequence by a violation of the assumption of homogeneity of subject error variance (F max-subjects = 2,45; df = 2 and 22; $p < ,05$). The assumption of homogeneity of subject variance being violated, a higher level of significance is used to evaluate the treatment sequence F value. Using a significance level of ,01, the obtained F value does not attain significance (F crit = 7,21) and it is concluded there is no effect due to treatment sequence.

The significant trials effect ($p < ,01$) is not affected by the above violation of the homogeneity of subject variance, and requires further analysis by means of Tukey HSD comparisons. The results of these comparisons are presented in Table 64.

TABLE 64 Tukey HSD Results for MCST Total Error Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	3,25	5,67 ($p < ,01$)
After 8 weeks		2,41

The results of Tukey HSD comparisons presented in Table 64 indicate that the significant trials effect is solely dependent on the decrease in total error scores between baseline assessment and assessment after 16 weeks ($p < ,01$).

5.2.5.4 Modified Card Sorting Test (MCST): Total Perseverative Error Scores

Mean MCST total perseverative error scores for the two treatment groups at the three times of assessment are presented in Table 65 and illustrated in Figure 24. The cell mean profile reveals similar scores for both groups at baseline and similar trends throughout the trial, with a sharp drop in the first trial period and a levelling off of this trend in the second trial period. The drop in the Sequence 2 group is much sharper than that in the Sequence 1 group. The results of statistical analysis of these mean perseverative error totals are presented in Table 66.

TABLE 65 Mean MCST Perseverative Error Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	4,19 (4,12)	2,42 (3,04)	2,00 (2,98)
Sequence 2 (A2)	4,38 (9,76)	1,43 (2,06)	0,90 (1,37)

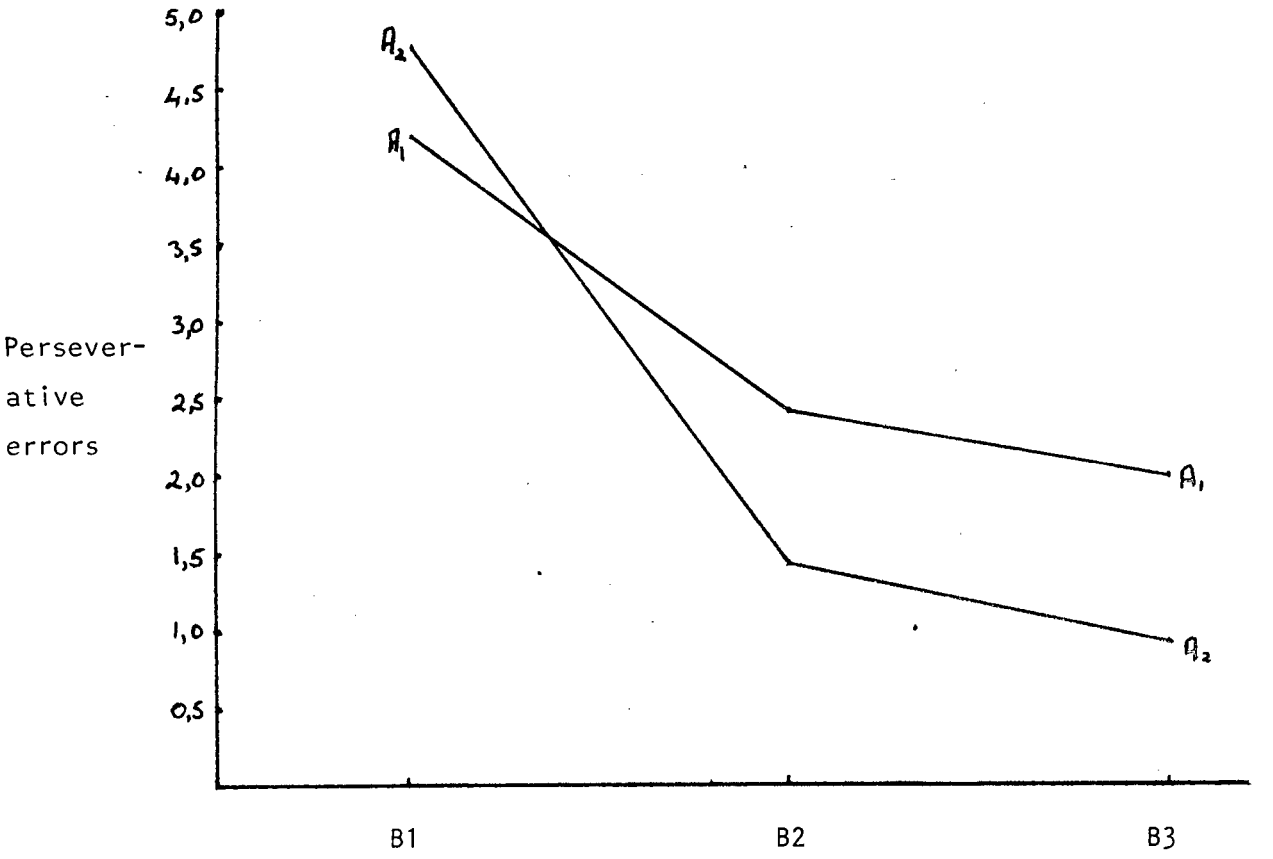


FIGURE 24: Modified Card Sorting Test - Perseverative Error Cell Mean Profile.

TABLE 66 Anova Summary Table of MCST Perseverative Error Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	14,00	0,41
Subjects	45	33,93	
Within subjects			
B. Time of assessment	2	107,11	7,00 ($p < ,01$)
AB. Interaction	2	5,92	0,39
Residual	90	15,31	

From Table 66 it can be seen that only the trials effect attains significance ($P < ,01$). The assumption of homogeneity of residual error variance is violated (F_{max}-residual = 4,48; df = 2 and 44; $p < ,01$). As before, a stricter test of significance is used ($p \leq ,01$), but the effect of time of assessment still attains significance using this stricter test of significance. Thus it is concluded that the effect due to time of assessment is real and that this therefore requires further analysis by means of Tukey HSD comparisons to determine the underlying structure of differences between levels of this factor. The results of these Tukey HSD comparisons are presented in Table 67.

TABLE 67 Tukey HSD Results for MCST Overall Perseverative Error Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	4,14 ($p < ,05$)	4,97 ($p < ,01$)
After 8 weeks		0,83

The results presented in Table 67 indicate that mean numbers of perseverative errors at baseline are significantly greater than those after 8 weeks ($p < ,05$) and after 16 weeks ($p < ,01$) although there is no significant decrement between 8 and 16 weeks. The major decrease in mean perseverative error scores occurs thus in the first trial period.

5.2.6.1 Selective Reminding List Learnings (SRLL): Mean Three Trial Total Scores

Mean SRLL three trial total scores for the two treatment groups at the three times of assessment are presented in Table 68 and illustrated in Figure 25. The cell mean profile reveals similar trends for both treatment groups, with a marked increase in total scores after 8 weeks followed by a greater decrease in total scores after 16 weeks, the gross effect over the entire trial being a moderate reduction in total scores. At both baseline and 16 weeks Sequence 1 subjects obtain higher scores, but at all times of assessment these intergroup differences are not

marked. The results of statistical analysis of these scores are presented in Table 69.

TABLE 68 Mean Selective Reminding List Learning Three Trial Totals (SRLL-TTT)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	41,62 (8,66)	45,19 (6,87)	37,77 (6,44)
Sequence 2 (A2)	39,95 (8,23)	45,59 (7,82)	35,95 (8,34)

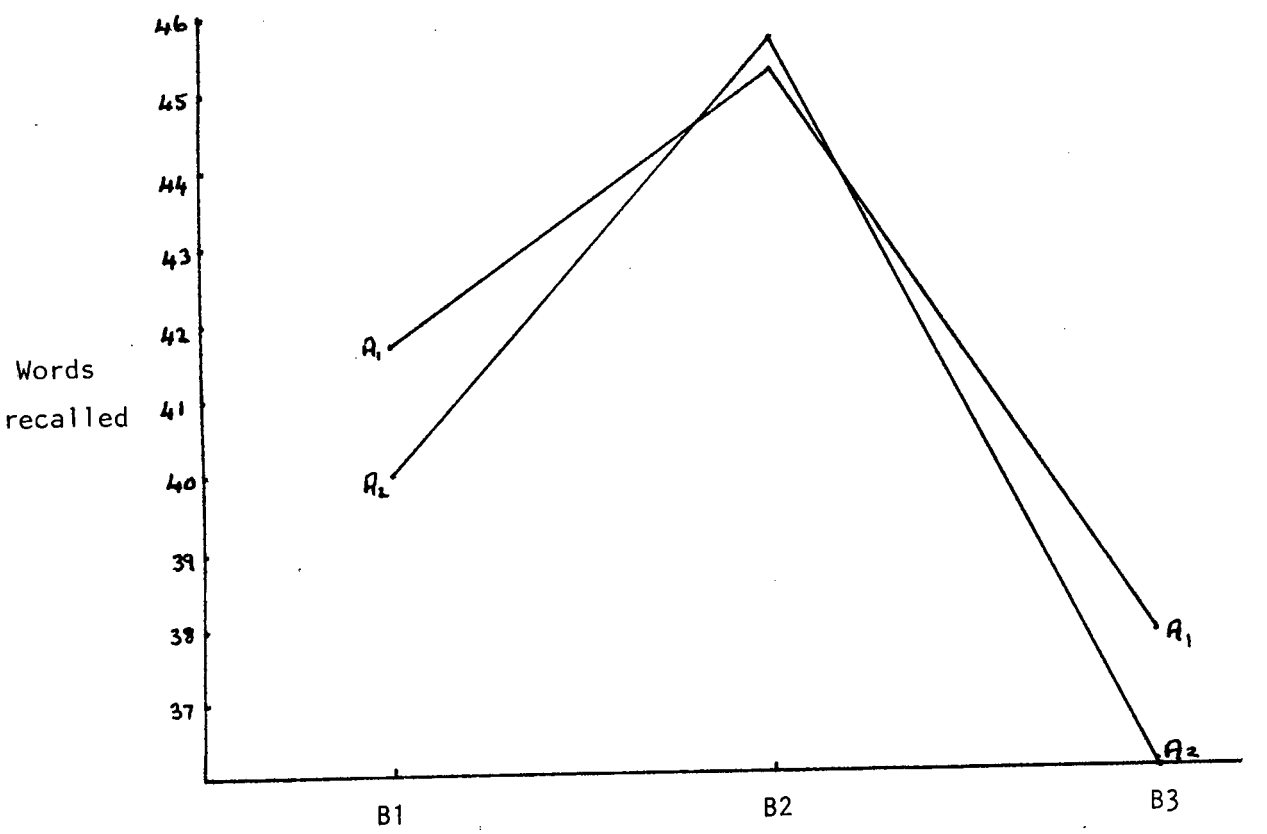


FIGURE 25: Selective Reminding List Learning Three Trial Total Cell Mean Profile.

From Table 69 it can be seen that only one effect attains significance. This is the trials effect ($p < ,01$). To ascertain the structure of differences underlying this effect, analysis by Tukey HSD comparisons is required. The results of these comparisons are presented in Table 70.

TABLE 69 Anova Summary Table for SRLL-TTT Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	37,61	0,29
Subjects	46	130,04	
Within subjects			
B. Time of assessment	2	868,87	35,15 ($p < ,01$)
AB. Interaction	2	18,20	0,74
Residual	92	24,72	

TABLE 70 Tukey HSD Results for SRLL-TTT Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-6,39 ($p < ,01$)	5,44 ($p < ,01$)
After 8 weeks		11,83 ($p < ,01$)

The results of Tukey HSD comparisons, presented in Table 70, indicate that highly significant differences exist between all times of assessment (all $p < ,01$). There is a significant increase in scores between baseline assessment and that after 8 weeks ($p < ,01$) followed by a more highly significant decrease in scores between 8 and 16 weeks ($p < ,01$). The difference between baseline assessment scores and those after 16

weeks also reflects a significant difference, in this case a decrease in scores ($p < ,01$).

5.2.6.2 Restrictive Reminding List Learning (RRLL): Mean Three Trial Total Scores

Mean RRLL three trial total scores for the two treatment groups at the three times of assessment are presented in Table 71 and illustrated in Figure 26. The cell mean profile shows that scores in both treatment groups follow similar trends throughout the trial. In both groups scores after 8 weeks reflect increased scores, but between the assessments at 8 and 16 weeks scores decrease by more than the degree of increase in the first 8 weeks, yielding an overall marked decrease in scores over the full trial period. At each time of assessment, Sequence 1 subjects achieve higher scores, though the differences are very small.

The results of statistical analysis of these scores are presented in Table 72.

TABLE 71 Mean Restrictive Reminding List Learning Three Trial Totals (RRLL-TTT)

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	42,73 (7,51)	46,08 (6,33)	38,00 (7,92)
Sequence 2 (A2)	42,36 (8,82)	44,68 (8,89)	36,09 (8,77)

From Table 72 it can be seen that there is only a significant trials effect ($p < ,01$). This requires further analysis by Tukey HSD comparisons to determine the underlying structure of differences in this factor. The results of these Tukey HSD comparisons are presented in Table 73.

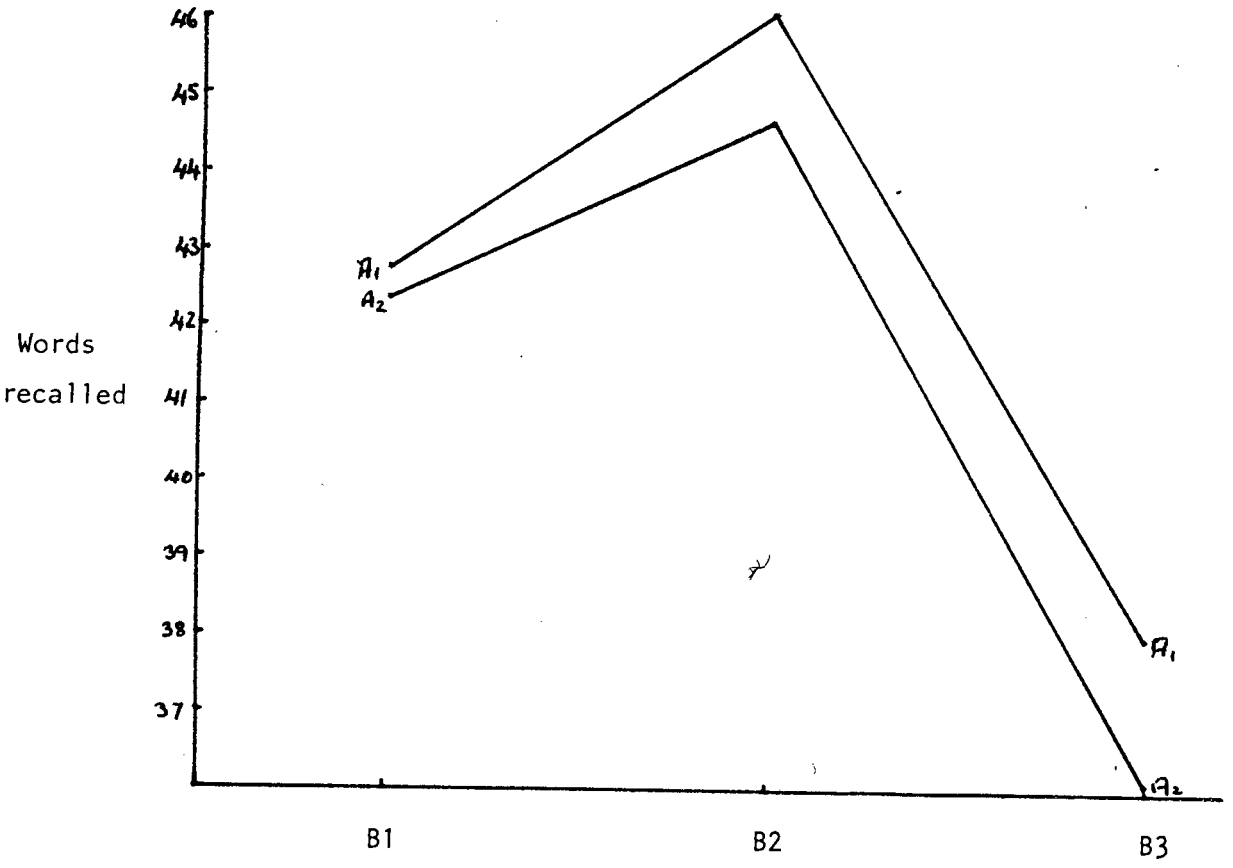


FIGURE 26: Restrictive Reminding List Learning Three Trial Total Cell Mean Profile.

TABLE 72 Anova Summary Table for RRLL-TTT Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	53,54	0,35
Subjects	46	153,09	
Within subjects			
B. Time of assessment	2	855,97	42,65 ($p < ,01$)
AB. Interaction	2	7,34	0,37
Residual	92	20,07	

TABLE 73 Tukey HSD Results for RRLL-TTT Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-4,35 ($p < ,01$)	8,46 ($p < ,01$)
After 8 weeks		12,82 ($p < ,01$)

The results shown in Table 73 indicate that all comparisons yield highly significant differences (all $p<,01$). There is a significant increase in scores after 8 weeks, but a significant marked decrease is observed after 16 weeks, which goes beyond the baseline level of scoring. The comparison between baseline scores and those after 16 weeks is also highly significant.

5.2.6.3 Selective Reminding List Learning (SRLL): Long Term Retrieval Scores

Mean SRLL long term retrieval scores for the two treatment groups at the three times of assessment are presented in Table 74 and illustrated in Figure 27. The cell mean profile reveals similar trends throughout the trial in the two groups, but a greater difference is visible after 16 weeks than at baseline of after 8 weeks, at which, for practical purposes, the two treatment groups score identically. At all times, Sequence 1 subjects achieve higher scores.

TABLE 74 Mean SRLL-Long Term Retrieval (SRLL-LTR) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	11,19 (4,61)	13,65 (3,84)	10,46 (3,26)
Sequence 2 (A2)	10,95 (3,66)	13,23 (4,32)	8,18 (4,23)

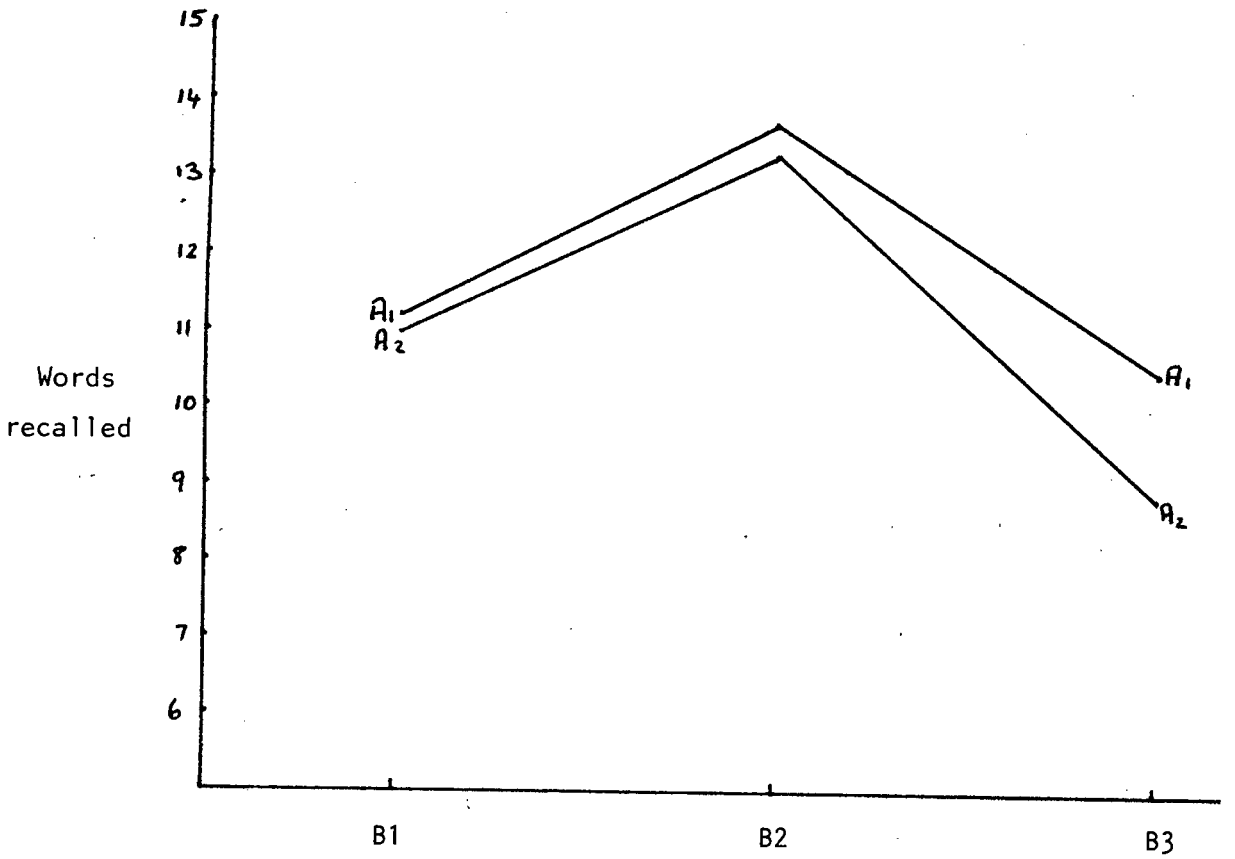


FIGURE 27: Selective Reminding List Learning Long Term Retrieval Cell Mean Profile.

Table 75 contains the results of statistical analysis of the SRLL long-term recall scores. Only the trials effect is significant ($p < ,01$). This is analysed by Tukey HSD comparisons to determine the differences underlying this significant effect.

Table 76 presents the results of Tukey HSD comparisons for SRLL long-term retrieval as a function of differences of time of assessment. All comparisons are significant. Scores increase significantly between baseline and assessment after 8 weeks ($p < ,01$) but decline to a greater extent between 8 and 16 weeks ($p < ,01$). The result of these two trends is a mean score after 16 weeks which is significantly lower than that at baseline ($p < ,05$).

TABLE 75 Anova Summary Table for SRLL-LTR Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	21,15	0,62
Subjects	46	33,92	
Within subjects			
B. Time of assessment	2	175,60	24,78 ($p < ,01$)
AB. Interaction	2	6,93	0,98
Residual	92	7,09	

TABLE 76 Tukey HSD Results for SRLL-LTR Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-8,84 ($p < ,01$)	3,79 ($p < ,05$)
After 8 weeks		10,00 ($p < ,01$)

5.2.6.4 Restrictive Reminding List Learning (RRLL): Long Term Retrieval Scores

Mean RRLL long term retrieval scores for the two treatment groups at the three times of assessment are presented in Table 77 and illustrated in Figure 28. The cell mean profile indicates parallel trends in the two groups during both periods of the trial, with Sequence 1 subjects attaining slightly higher scores at each time of assessment.

TABLE 77 Mean RRLL Long Term Retrieval (RRLL-LTR) Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	13,77 (4,08)	15,58 (3,07)	11,54 (3,72)
Sequence 2 (A2)	13,18 (3,97)	14,55 (4,08)	10,27 (3,51)

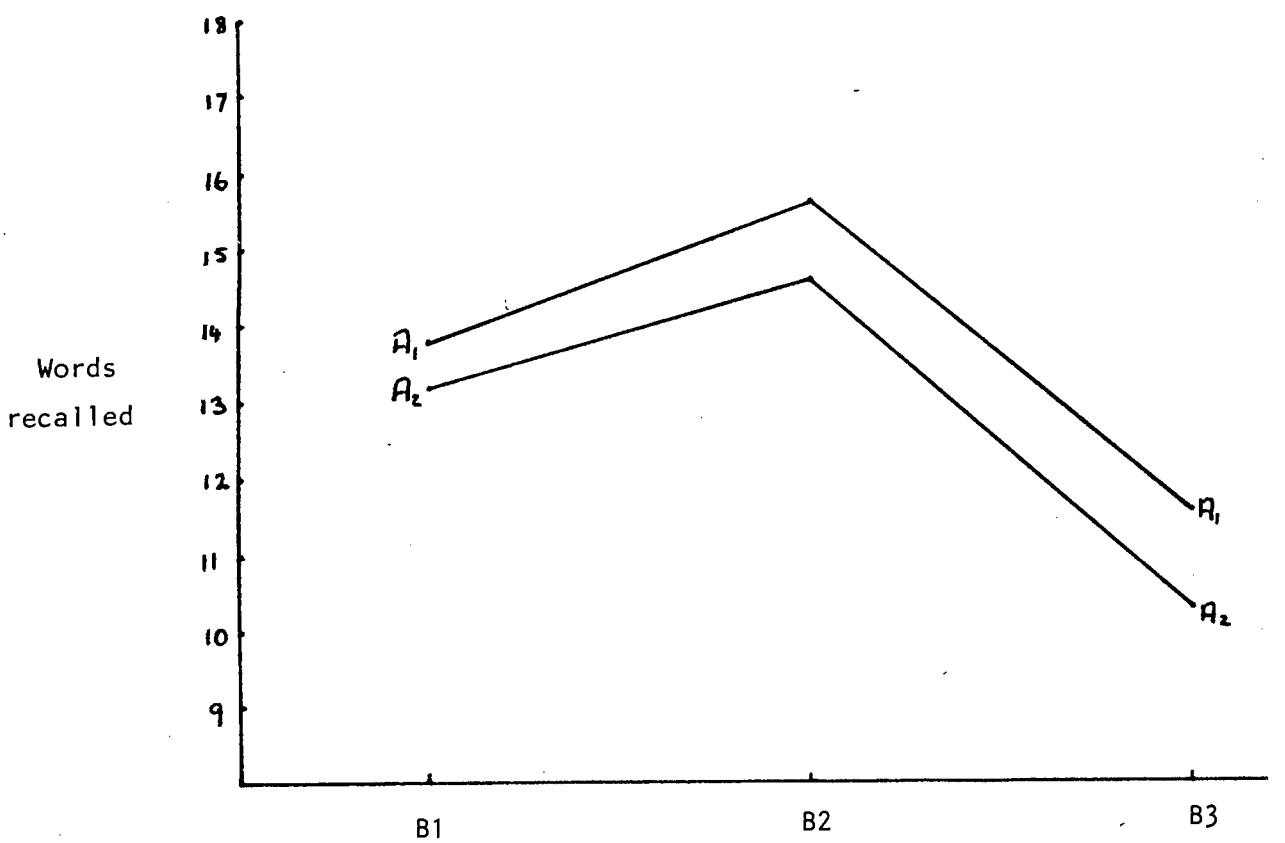


FIGURE 28: Restrictive Reminding List Learning Long Term Retrieval Cell Mean Profile.

Table 78 presents the results of statistical analysis of the above data. The only significant effect is that of trials ($p < ,01$), which requires further analysis by Tukey HSD comparisons to determine the structure of underlying differences.

TABLE 78 Anova Summary Table for RRLL-LTR Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	33,05	1,02
Subjects	46	32,31	
Within subjects			
B. Time of assessment	2	209,64	42,64 ($p < ,01$)
AB. Interaction	2	1,41	0,29
Residual	92	4,92	

TABLE 79 Tukey HSD Results for RRLL-LTR Overall Means at Each Assessment

	After 8 weeks	After 16 weeks
Baseline	-4,97 ($p < ,01$)	8,03 ($p < ,01$)
After 8 weeks		13,00 ($p < ,01$)

From Table 79 it is evident all comparisons are highly significant. There is a significant increase in scores between baseline assessment and the assessment after 8 weeks ($p < ,01$) and a highly significant decrease in scores between 8 weeks and 16 weeks which more than negates the preceeding increase ($p < ,01$). The final score after 16 weeks is significantly lower than that at baseline ($p < ,01$).

5.2.7.1 Serial 3s: Total Enumerations

Mean Serial 3s total enumeration scores for the two treatment groups at the three times of assessment are presented in Table 80 and illustrated in Figure 29.

TABLE 80 Mean Serial 3 Total Enumerations Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	13,69 (7,27)	14,65 (7,79)	15,38 (7,27)
Sequence 2 (A2)	15,00 (6,35)	16,18 (7,00)	14,86 (6,56)

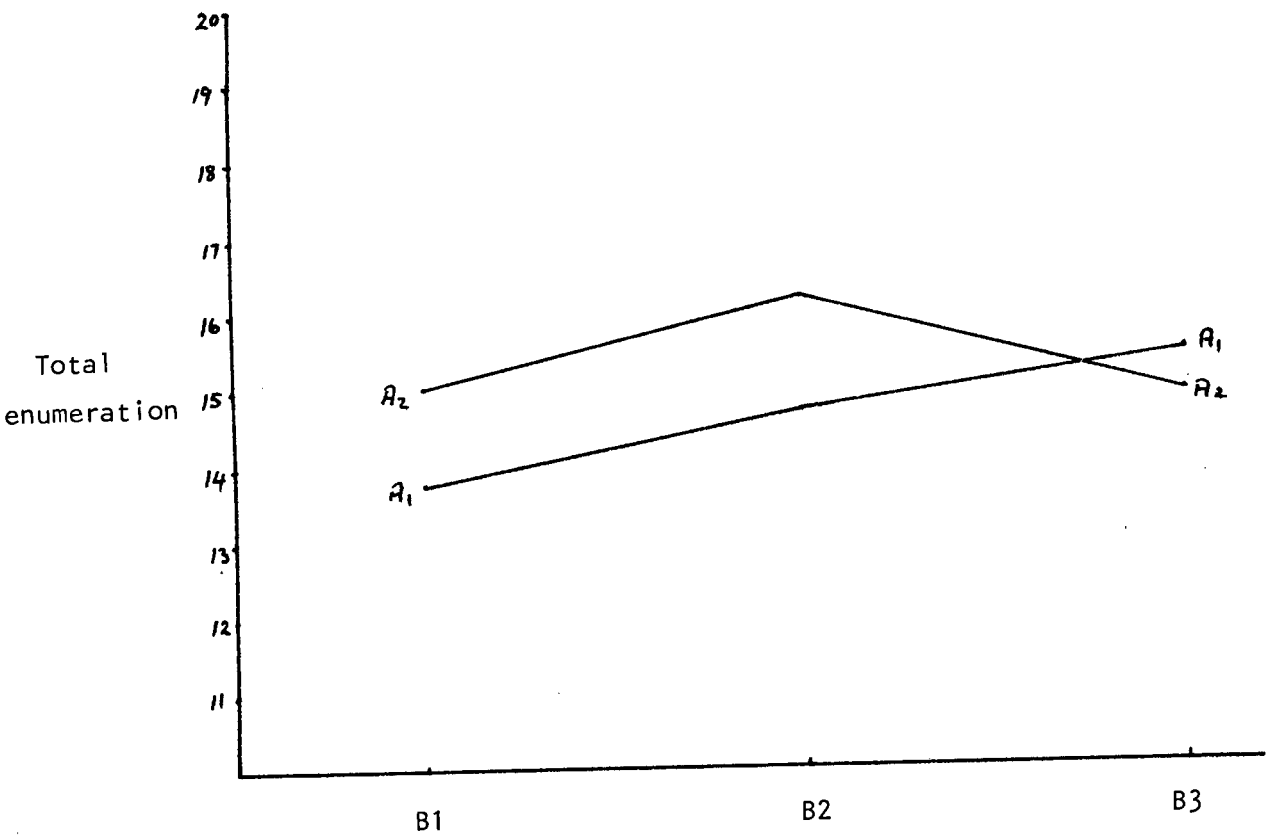


FIGURE 29: Serial 3s Total Enumeration Cell Mean Profile.

The cell mean profile (Figure 29) shows that at baseline Sequence 2 subjects obtain higher scores, with this difference carrying through to the assessment after 8 weeks, at which both mean scores are moderately increased. Between the second and third assessments, differing trends are evident. Sequence 1 subjects continue to moderately increase scores while Sequence 2 subjects scores decrease to their previous baseline level. Results of statistical analysis of these scores are presented in Table 81.

TABLE 81 Anova Summary Table for Serial 3s Total Enumeration Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	21,28	0,15
Subjects	46	138,58	
Within subjects			
B. Time of assessment	2	14,62	2,38
AB. Interaction	2	15,08	2,46
Residual	92	6,14	

The results presented in Table 81 show that no significant influences are active on Serial 3s total enumeration scores. No further analysis is possible.

5.2.7.2. Serial 3s: Error Scores

Mean Serial 3s total error scores for the two treatment groups at the three times of assessment are presented in Table 82 and illustrated in Figure 30.

TABLE 82 Mean Serial 3s Error Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	0,65 (0,89)	0,85 (0,97)	0,46 (1,03)
Sequence 2 (A2)	0,59 (1,01)	0,82 (1,01)	0,77 (1,11)

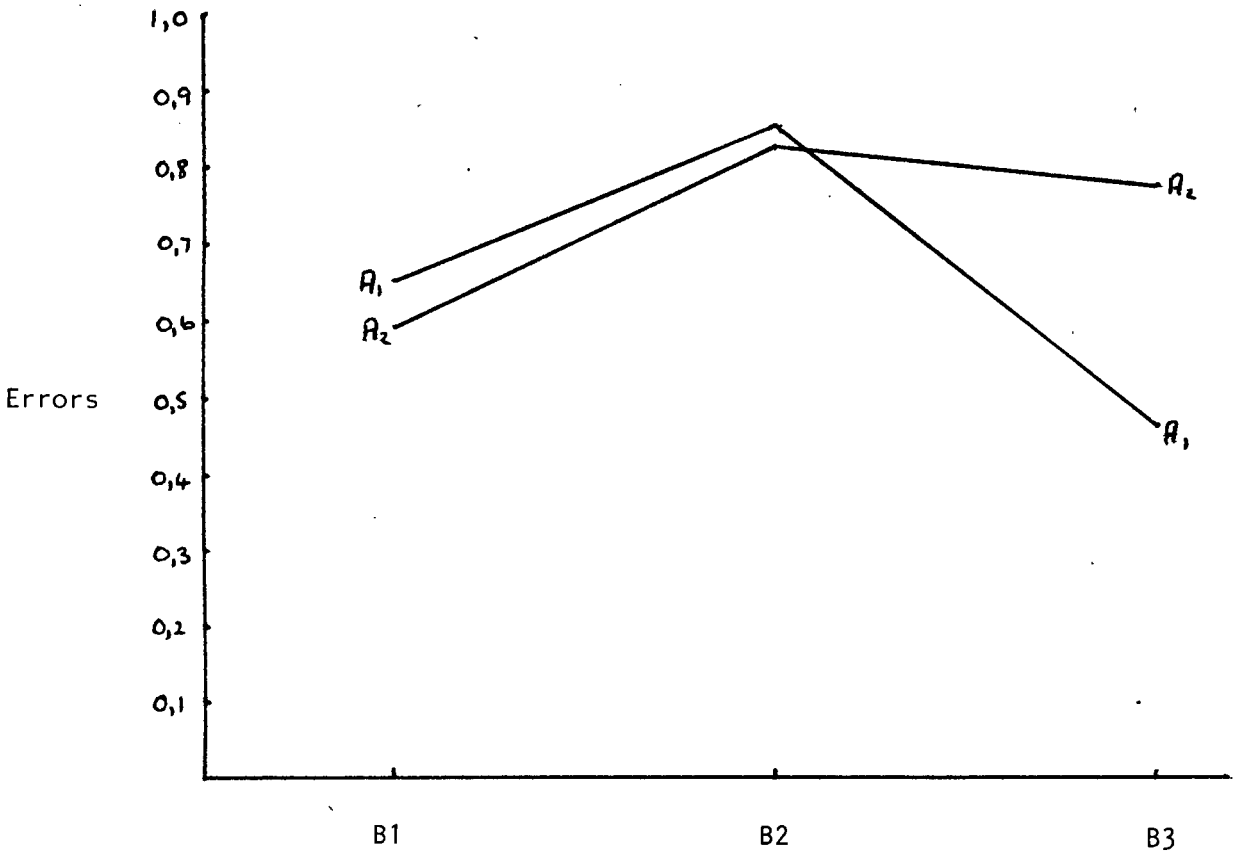


FIGURE 30: Serial 3s Error Scores Cell Mean Profile.

The cell mean profile (Figure 30) reveals slightly higher scores at baseline in the Sequence 1 group. Error scores increase approximately equally in each treatment group between the baseline assessment and assessment after 8 weeks. After the eighth week the group trends differ, with scores of Sequence 1 subjects dropping sharply to a level below the baseline score for this group, while scores of Sequence 2 subjects drop very slightly and remain above the baseline scores. The results of statistical analysis of the data are presented in Table 83.

TABLE 83 Anova Summary Table for Serial 3s Error Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	0,19	0,16
Subjects	46	1,23	
Within subjects			
B. Time of assessment	2	0,72	0,81
AB. Interaction	2	0,51	0,57
Residual	92	0,89	

The results presented in Table 83 indicate that no significant trends are active in Serial 3s total error scores. No further analysis is possible.

5.2.7.3. Serial 3s: Total Correct Enumerations

Mean Serial 3s correct enumeration total scores for the two treatment groups at the three times of assessment are presented in Table 84 and illustrated in Figure 31.

TABLE 84 Mean Serial 3s Correct Enumeration Totals

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	13,04 (7,66)	13,81 (8,02)	14,92 (7,47)
Sequence 2 (A2)	14,41 (7,03)	15,36 (7,27)	14,09 (7,10)

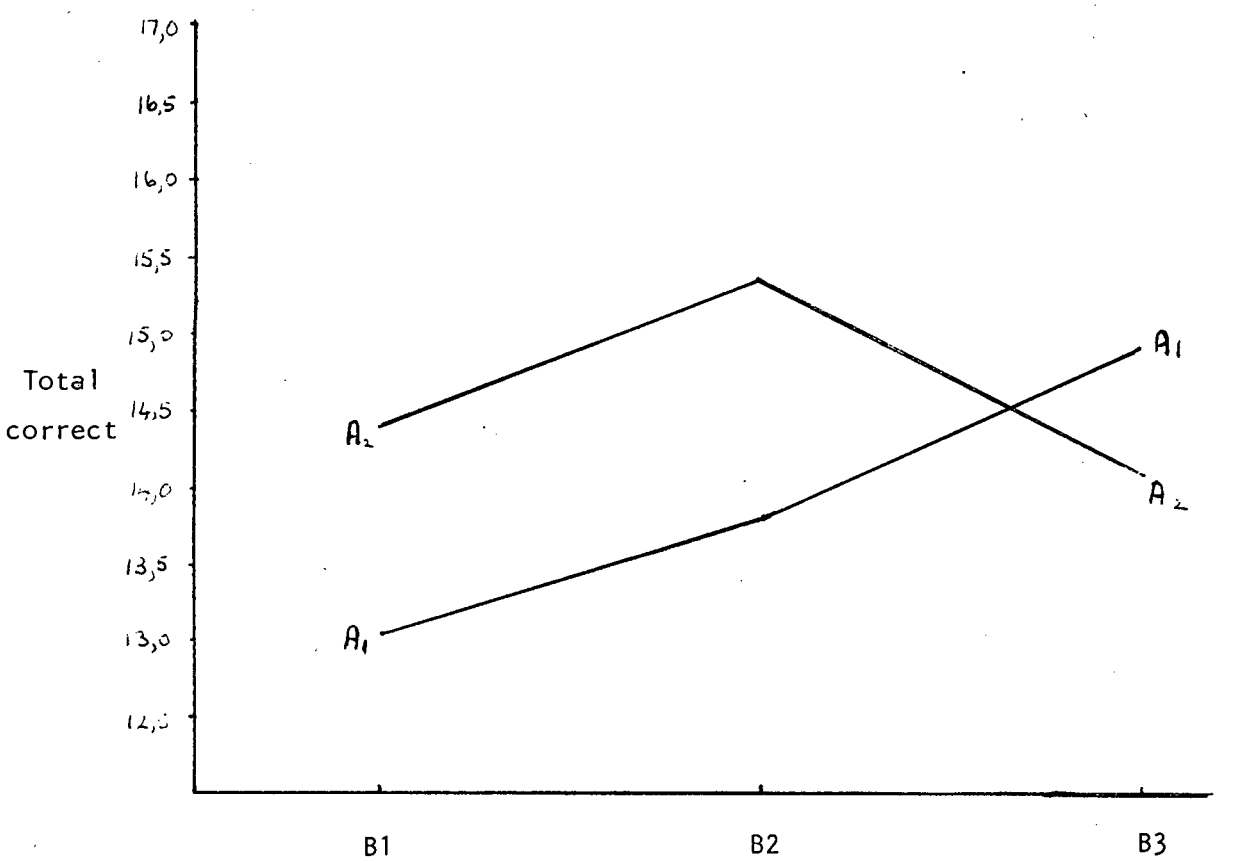


FIGURE 31: Serial 3s Correct Enumeration Cell Mean Profile.

The cell mean profile (Figure 31) indicates that scores are markedly greater at baseline in the Sequence 2 group. Scores in both groups are equally increased after 8 weeks, but differing trends are evident between the assessment at 8 weeks and that at 16 weeks. Sequence 1 subjects' scores continue to increase at a slightly sharper rate than previously, while Sequence 2 subjects' scores decrease sharply to score slightly below that obtained for this group at baseline.

The results of statistical analysis of the data are presented in Table 85.

TABLE 85 Anova Summary Table for Serial 3s Correct Enumeration Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	17,42	0,11
Subjects	46	153,36	
Within subjects			
B. Time of assessment	2	10,82	1,61
AB. Interaction	2	21,03	3,14 ($p < ,05$)
Residual	92	6,70	

Table 85 reveals a significant interaction effect ($p < ,05$) which requires analysis of simple main effects. The results of these analyses are presented in Table 86.

TABLE 86 Simple Main Effects Summary table for Serial 3s Correct Enumerations Totals

Source	df	MS	F ratio
A at B_1	1	22,4	0,40
A at B_2	1	28,6	0,51
A at B_3	1	9,77	0,18
Within	138	55,99	
B at A_1	2	23,14	3,45 ($p < ,05$)
B at A_2	2	10,56	1,58
Residual	92	6,70	

Table 86 reveals that only the simple main effect of B at A_1, that is, the effect of time of assessment in the Sequence 1 treatment group, is significant ($p < ,05$). The results of Tukey HSD comparisons of cell means for this treatment group are presented in Table 87.

TABLE 87 Tukey HSD Results for the Effects of Treatments on Serial 3s Correct Enumerations Total Scores in Group 1 (piracetam-placebo order)

	After 8 weeks	After 16 weeks
Baseline	-1,51	-3,69 ($p < ,01$)
After 8 weeks		-2,18

The results presented in Table 87 indicate that the significant simple main effect of time of assessment in the Sequence 1 treatment group is solely dependent on the difference between scores at baseline and scores after 16 weeks ($p < ,01$).

5.2.8 Inglis Paired Associate Learning Test (IPALT)

Mean numbers of presentations of stimulus words required to complete the Inglis Paired-Associate Learning test for the two treatment groups at the three times of assessment are presented in Table 88 and illustrated in Figure 32.

TABLE 88 Mean Inglis Paired Associate Learning Test Presentations Scores

	Baseline B1	After 8 weeks B2	After 16 weeks B3
Sequence 1 (A1)	8,88 (5,54)	6,27 (4,49)	6,46 (4,28)
Sequence 2 (A2)	14,95 (13,45)	9,09 (6,42)	8,95 (12,63)

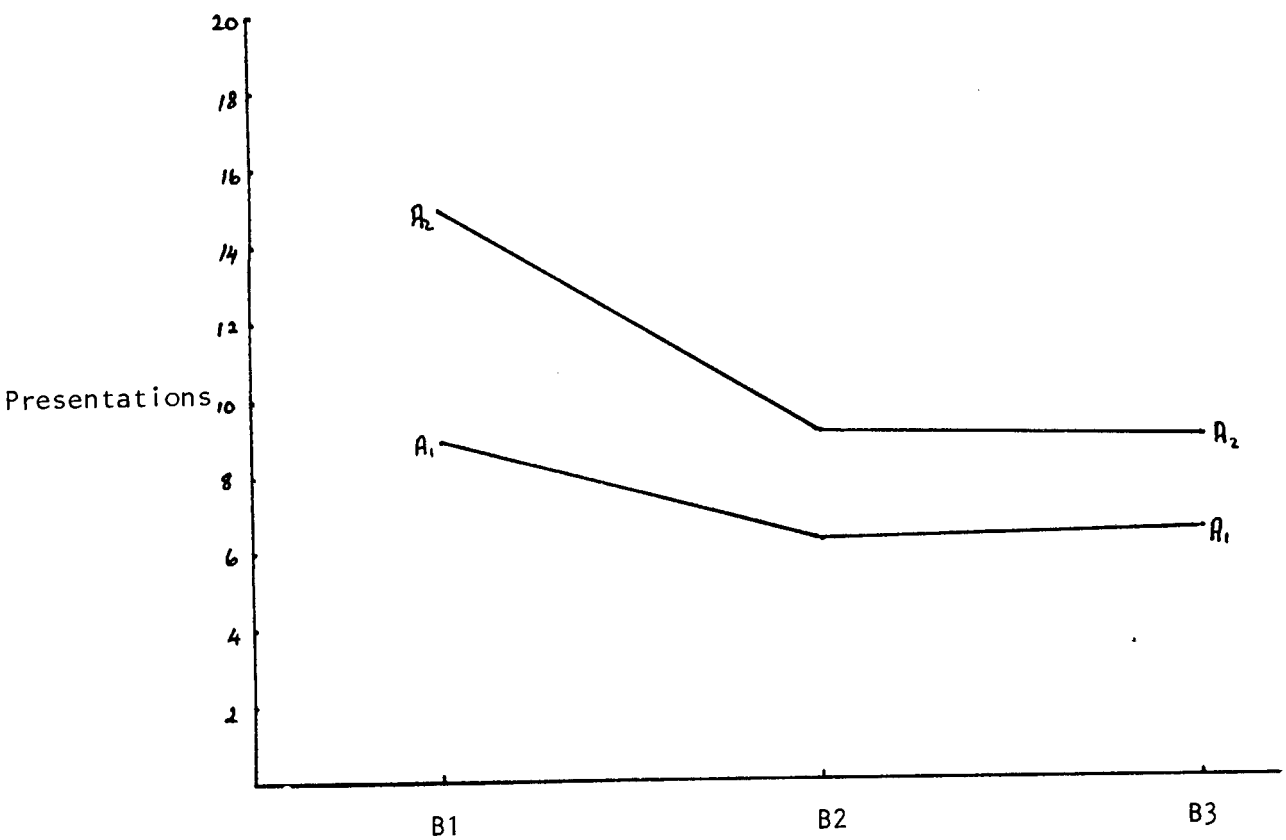


FIGURE 32: Inglis Paired-Associate Learning Test Presentations Cell Mean Profile.

The cell mean profile indicates that Sequence 2 subjects require substantially more presentations at baseline, but the difference is reduced after 8 weeks. Between baseline and the assessment at 8 weeks numbers of presentations are reduced in both groups but more so in the Sequence 2 group. Between assessments after 8 and 16 weeks the required numbers of presentations level off equally in both groups.

The results of statistical analysis of the data are presented in Table 89.

TABLE 89 Anova Summary Table For IPALT Presentations Scores

Source	df	MS	F ratio
Between subjects			
A. Treatment sequence	1	514,84	5,42 ($p < ,05$)
Subjects	46	95,06	
Within subjects			
B. Time of assessment	2	283,71	4,86 ($p < ,05$)
AB. Interaction	2	46,58	0,80
Residual	92	58,36	

The results presented in Table 89 show that there is no significant interaction but that there are significant effects of treatment sequence ($p < ,05$) and time of assessment ($p < ,05$).

However, the assumption of homogeneity of error variance is violated for both subject error variance (F max = 3,35; df = 2 and 22; $p < ,01$) and residual error variance (F max = 9,76; df = 2 and 44; $p < ,01$).

A more stringent test of significance is required to compensate for the violation of F max. Using a probability level of $p \leq ,01$, neither main effect achieves significance. No further analysis is possible.

6. DISCUSSION

6.1 EVALUATION OF STATISTICAL RESULTS

Of the 31 statistical analyses of test data, only two yielded the interaction effects required to support a contention of differential effects of piracetam and placebo on functional performance as assessed by psychometric instruments. The two analyses concerned were those for scores on the WAIS Block Design test ($p < ,01$) and for scoring of total correct responses on the Serial 3s subtraction task ($p < ,05$). Inspection of the cell mean profile for the Block Design test (Figure 18) reveals moderate increases, reflecting improvements, in both groups after placebo treatment. In both groups, performance after piracetam treatment remained roughly constant, in fact, from Table 46 it can be seen that performance in both groups deteriorated slightly after piracetam treatment.

The significant interaction effect thus reflects superior (improved) performance on the Block Design test when placebo was administered, while piracetam treatment proved less useful. It is notable however that the simple main effect for A at B1 (Table 48), i.e. the comparison between the two groups at baseline, is significant ($p < ,05$). As subjects were randomly assigned to treatment groups this result is unexpected, as the groups should be approximately equal at baseline on all measures. This simple main effect can thus be attributed to the chance factors (RSV).

The difference between the mean Block Design scores of the groups after 16 weeks was approximately equal to that at baseline, reflecting equal gains over the trial period, the full extent of these gains being due to the effects of placebo alone. While the similarity of the trends in both groups under each treatment, is clear from Figure 18, the influence of the pre-existing difference in baseline scores on the significance of the interaction effect is not clear. It might be this difference enhanced an otherwise non-significant interaction effect. This result

should therefore be interpreted with caution.

Inspection of Figure 31, the cell mean profile for the total of correct responses in the Serial 3s subtraction task, indicates no differences in trends during the first trial period, where equal score increases, reflecting improvements, were observed. Trends differed in the latter trial period, however, where scores for the group receiving piracetam treatment continued to improve, while scores for placebo-treated subjects deteriorated. Analysis of simple main effects (Table 86) reveals that the difference underlying the significant interaction effect was solely to be found within the scores of the group receiving piracetam after the placebo. Table 87 reveals that this was the cumulative difference alone between baseline scores and those after 16 weeks within this group.

This result provides partial support for an interpretation that piracetam increases concentration, when compared to placebo. However, the fact that this only occurred in one half of the trial, while no difference was observed in the first period of the trial, weakens this argument, and suggests the possibility that this too is a result of chance factors.

As the 5% level of significance was used for the 31 analyses, statistically significant values , resulting purely from the operation of chance may be expected in 1,55 of the interaction effect values. As these events are discrete however, it is probable that two such results should be obtained. It thus appears that the sole two significant interaction effects can be attributed to chance factors. This interpretation is supported by the fact that opposed findings result from these analyses, the analysis of Block Design scores indicating superiority of placebo over piracetam, while the analysis of total correct response scores for the Serial 3s subtraction task indicates marginal superiority of piracetam over placebo. Although a non-directional hypothesis was used, uniformity of the direction of differences could be expected if real differences existed between effects.

Of the remaining analyses, 10 yielded no significant effects whatsoever, while a further 18 results indicated score changes over the trial period irrespective of treatments administered. Should the interaction effect for Block Design scores be regarded as non-significant, the main effects for this analysis may be interpreted, in which case the number of significant B-effects is increased to 19.

Significant A-effects were not anticipated in this study, as the use of randomized group assignment procedures should have made the groups approximately equal at baseline, and subsequent treatments administered, though in opposite sequences for the two groups, were equivalent. Taking into account the significant A-effect in the Block Design analysis, three A-effects attained statistical significance. Inspection of the cell mean profiles for these analyses (Figures 18, 22 and 23) reveals marked differences between groups at baseline in all cases. The magnitude of the difference is seen to persist, with minor variations, throughout the trial period. Thus the baseline differences, which are chance effects, are the sole determinants of the significant A-effects. The number of these A-effects, three, differs only slightly from the expected value of two, determined on statistical grounds. Consequently, these significant A-effects may all be attributed to chance.

The above results show no differences between the effects of piracetam and those of placebo on the functional capacities of chronic alcoholics. All the interaction effects and effects reflecting overall differences between treatment groups may be attributed to chance. The single regular, though by no means consistent, finding is that of significant changes in scores over time irrespective of treatments administered. This was expected, as the two way anova with repeated measures is known to be extremely sensitive to such changes (Gilbert, 1977c).

In a repeated measures design improvements must be anticipated to degrees varying with the nature and difficulty of each measure, due to the effects of practice, subtle shifts in the nature of functions assessed at retests, growing test sophistication including changing

test-taking attitudes and lessening anxiety, and perceived demand effects, quite apart from any real effects due to treatments. In this study the failure to achieve significant interaction effects indicates that varying the treatments administered failed to significantly influence test performance, and thus the changes in scores in each group for each period are attributable to the same factors, and to all intents, the two groups can be joined and their scores contrasted at the three assessments.

Further interpretation of significant effects due to changes in scores over the trial period falls outside the scope of this study, as it is implicit in these analyses that there are no differences between the treatments administered.

Overall, the results of statistical analyses indicate that no differences exist between the effects of piracetam treatment and placebo treatment. The interaction effects observed may be attributed to chance, as can the apparent effects of treatment sequences (A-effects) which on inspection are found to depend almost exclusively on baseline differences between treatment groups. The only authentic effects (including, however one or two anticipated but unidentifiable chance effects) are those reflecting changes between assessments, indicative of practice and the above mentioned related effects, while denying any differences between subjects treated with piracetam and those treated with placebo.

These results indicate that piracetam has no effects beyond those perceived demand effects engendered by the receipt of treatment of any kind, that is, the effects of piracetam on scores obtained from this psychometric battery appear equivalent to placebo effects, and no more.

6.2 EVALUATION OF THE INTERNAL VALIDITY OF THIS STUDY

The placebo-controlled, randomized double blind cross-over design constitutes probably the most powerful test of drug effects in chronic

conditions. This is especially so in the case of piracetam, which has no known side effects to betray the double-blind procedure. The design controls bias in test administration and holds subject expectations constant. In addition, the delay, in this study, in scoring test data until all subjects had completed the trial prevented bias in test administration at later assessments. Added to this, subject protocols were broken only after the completion of scoring, thus eliminating the possibility of bias in scoring. Consequently, it may be assumed that objectivity was ensured in both test administration and scoring.

In terms of life events which might have influenced subjects' performances, it is presumed that, while these can not be eliminated in a long duration trial involving out-patients, these influences should be equally distributed across the two groups as a consequence of randomized assignment. Similarly, it is hoped that any undetected non-compliance should be held constant across groups by the same procedure. It was intended to use unconsumed pill returns as a check on consumption, albeit this is a poor method vulnerable to deliberate falsification. However, many subjects omitted to return these, despite reminders, but confirmed they had consumed the bulk of their supplies. (As subjects were selected for reliability, the probability of deliberate falsification of consumption is likely to be minimal.) Once again, randomization serves to hold the uncertainty of compliance constant, as its elimination was not possible. The high dosages given in this trial also militate against minor non-compliance. The question of conducting blood assays was investigated, as this would be the best check on recent compliance, though it could not provide information about the full 6 week period. However the facilities were not available locally, and such were the difficulties and costs of preserving and transporting samples, as well as analysing these, that it was decided not to proceed with these.

While high degrees of variability of scores might result from the heterogeneity of influences and degrees of compliance possible under the randomization control, these should mainly influence between-subject

variance, which is not used to assess the significance of interaction and trials effects, so it does'nt seem that this has suppressed any interaction effects. This may be argued in any event from the fact that so many trials effects attained statistical significance, despite changes in scores of very minor magnitude, as seen in cell mean profile graphs (e.g. see Figures 12, 13 and 16). Further, the absence of differences between treatment effects can not be ascribed to test insensitivity, as the statistical significance of so many B-effects demonstrates, at the very least, that the measures in question were capable of reflecting performance changes. Thus treatment effects should be detectable on these measures, if not on the rest. This was not the case. Another methodological strength is that the periods between assessments were long enough (6 weeks plus or minus 10 days) to ensure that each assessment was uncontaminated by the effects of the alternative treatment. (This point pertains only at the final assessment, when both treatments have been administered.)

The majority of subjects were receiving some form of medication before entering the trial, and they were instructed not to change these for the duration of the trial. No major medication changes were reported, and consequently it can be assumed that this could not have biased results. As the subjects had proved themselves "reliable" to the satisfaction of the hospital, the possibility of unreported medication changes must be very small. Groups did not differ significantly in terms of numbers of subjects receiving psychotropic medication (see Appendix 18). Statistically, there is little chance any real interaction effects were missed, as the sample size and the nature of the design combine to limit the possibility of both Type I and Type II errors to 5%, while the analysis was capable of detecting relatively small differences (see Appendix 19).

Consequently there is little possibility of systematic bias influencing test scores, and on statistical grounds there is little chance of incorrect decisions being made in individual statistical analyses, although collectively chance significant results can be expected due

to the number of analyses performed.

There appear to be insufficient grounds to challenge the internal validity of this study. This being so, the question of the external validity of the findings requires consideration.

6.3 THE EXTERNAL VALIDITY OF THESE FINDINGS

Within the alcoholic population, alcoholics free of episodes of problem drinking for long periods constitute a minority. In addition to this, advancing age has frequently been shown to interact with the effects of alcohol abuse in producing morphological and functional deficits, and hence it would be advisable to restrict generalisations to alcoholics of similar ages. As can be seen in Table 1, the mean age of this sample at commencement of this study was 48 years. In terms of the studies on alcoholism reviewed previously, this should be described as a sample of "middle-aged" or "older" alcoholics. It would be expected that this sample would exhibit greater deficits relative to premorbid status than would a sample of younger alcoholics.

Generally, studies have not consistently reported significant relationships of drinking variables with the extent of functional and morphological abnormalities. Very probably this is due to the fact that the relevant information has to be obtained from the alcoholic personally, and as a consequence of the deficits suffered by the alcoholic, this information is vague and inaccurate. In addition, it is known that alcoholics frequently deliberately minimize in reports of consumption and related variables (Knox, 1980). As a result, it is unlikely that it be necessary to restrict these findings to alcoholics with similar drinking histories. The criterion of a minimum of 10 years history of problem drinking used in this study should be considered merely as a guarantee of the accuracy of a diagnosis of chronic alcoholism.

Subjects were selected for this trial if they were considered by the

hospital to be reliable in attending hospital appointments. This criterion was regarded as desirable to counteract the possibility of a high drop-out rate, as these are frequently encountered in studies involving alcoholics (e.g. Clarke and Haughton, 1975; Klisz and Parsons, 1979; Ron, 1982). This means that the alcoholics in this study constituted a selected group. While it is probable that the variables related to "reliability" are predominantly personality variables, it is possible that cognitive variables might be implicated. It can be argued, however, that even should cognitive variables relate to this criterion, this should reflect a difference, relative to other alcoholic groups, in the degree of impairment suffered, rather than a total absence of impairment. No accurate measures of premorbid levels of functioning are available, but it can be contended from previously cited literature, indicating widespread prevalence of both morphological and functional deterioration in chronic alcoholics, the incidence of detection of which rises with age, that, at the mean age of the present sample, the occurrence of impairments in the majority of subjects should be beyond question.

The issue under investigation here is the extent of change possible under the action of piracetam. Consequently, even if this sample should prove to be functionally more normal than other alcoholics, this in no way detracts from the findings, as improvements have been claimed even for normal subjects (Lagergren and Levander, 1974; Dimond, 1975; and Demay and Bande, 1980). Subjects suffering functional deficits merely offer greater opportunity of avoiding "ceiling effects" limiting the extent of improvement. The possibility of this sample differing markedly on functional variables from other alcoholic samples seems limited, as the literature indicates limited and protracted improvement with continuing abstinence, with marked deficits compared to normal subjects after as much as 30 or more months of abstinence (Adams et al., 1980; Ron, 1982). Thus it appears warranted on these grounds to accept that the alcoholic sample used in this study was indeed functionally impaired, and thus still represents the abstinent alcoholic population.

Finally, it must be noted that the sampling method used was not random, thus it is possible that the sample was biased in some unknown way, and may not accurately represent the abstinent alcoholic population. Indeed some bias is almost certain, as all subjects were drawn from one institution. While this may be so, it must be stated that samples of convenience are the rule rather than the exception in drug trials, and that truly random sampling is extremely rare in studies of clinical populations. On these grounds it may be stated that the claims of this study are of equivalent stature to other studies in related fields. In a case of this nature, where it appears likely that morphological abnormalities underlie the observed functional deficits in an unknown way, it appears probable that the contention of presence of abnormalities is less contestable, and thus inaccuracies resulting from differences between samples should at most reflect quantitative rather than qualitative differences at a functional level.

6.4 IMPLICATIONS FOR PIRACETAM'S EFFICACY IN TREATING FUNCTIONAL DEFICITS IN CHRONIC ALCOHOLISM

This was the first study of piracetam's effects on abstinent alcoholics, that is, alcoholics free of the acute effects of drinking. As such, the study is unique, and the conclusions drawn from it should be regarded as tentative until replication studies have been performed. As is the case with the majority of drug trials, this is especially the case as non-random sampling was used, and thus the representativeness of the sample is uncertain. The results indicate no differences between piracetam and placebo in treatment of functional deficits in abstinent alcoholics, the two statistically significant interaction effects resulting from the effects of chance. The conclusion drawn from this, that piracetam has no beneficial effects for abstinent alcoholics over and above those motivational and psychological effects resulting merely from receipt of treatment in itself, is at variance with those drawn by Binder (1974) and Binder and Doddabela (1976), but as implied above, there are differences between these studies and

the present one which might account for this.

It appears that Binder (1974) and Binder and Doddabela (1976) both studied recently detoxified alcoholics, although this was not explicitly stated in the latter study. While this might mean that gross withdrawal symptoms had subsided it does not mean that subjects had completed that sharp improvement in functional capacities which is known to occur in the first two to three weeks of abstinence (Page and Linden, 1974; Page and Schaub, 1977). Thus, differing rates of improvement, possibly resulting from random sampling variation, might erroneously be attributed to treatment effects. This might particularly be the case in Binder's (1974) blind one-period clinical trial, while Binder and Doddabela's (1976) double-blind cross-over study, though less susceptible to this failing, may still have been influenced by it.

Dosages do not vary between these studies, nor do sample sizes and treatment periods vary much. Binder's (1974) sample was exclusively male, making it very similar to that used in the present study, but Binder and Doddabela (1976) neglected to mention the sexual composition of their sample. As both studies utilized in-patients, it might be possible to assume similar composition. (Generally the vast majority of alcoholic in-patients are male.) If this is so, it is unlikely that the cause of the different results originated here. The present study however involved out-patients, and this could contribute to the differing findings. Out-patients are subject to a wide range of environments and experiences, and hence their performance may be more variable, and less treatment-related. On the other hand, should any form of contamination occur, e.g. a negation of the blind procedures, the effects would more easily spread through the greater contact between in-patients.

The possibility of contamination of these in-patient studies is substantial, as, if pills were chewed instead of being immediately swallowed (as recommended), it would be found that piracetam tasted different to the placebo, though in all other respects the two were

identical. The communication of this difference among in-patients during the various periods of the trial, combined with their interpretations of the demand characteristics of these differences, could result in total negation of subject blindness. It is not impossible that subjects might reason that a placebo or "sugar pill" might be bland and near tasteless, and that the pill with the bitter taste was more likely to be the active substance, as was indeed the case. This would result in greater motivation in the latter case. In Binder's (1974) study subjects were informed that confirmation of beneficial effects of piracetam treatment could result in early discharge, so subjects can be considered to have been highly motivated to respond "correctly".

A related failure in Binder's (1974) study is the fact that after baseline testing subjects themselves drew lots to decide which subjects received placebo and which received piracetam. As the design was described as "blind", it should be possible to assume that the subjects were not informed of the purpose of drawing lots. However, the procedure has demand characteristics, and should not have been adopted, as in conjunction with the above-mentioned factors, it increased the chances of contamination of the results. It is also possible that, owing to the absence of double-blind procedures, scoring might have been less objective than in Binder and Doddabela's (1976) and the present trials. Binder's (1974) conclusions were based on significant results obtained on two of the four tests administered. As with the Benton Visual Retention and Beck tests, which yielded non-significant results, were claimed to measure "stimulus-response" abilities, Binder concluded that piracetam had no effect on such narrowly circumscribed functions, but acted on more complex cerebral functions, characterized by co-ordination and co-operation of discrete functions. These were measured by the Pauli and Chapius tests. However, Binder provided no details for scoring these tests, though the results were presented in categorizations of "deteriorated", "improved" and "unchanged". Most significant results barely achieved the 5% level of significance, and the question must be raised, in the light of the

single blind design used, as to the objectivity of these categorizations. It might be argued that raw scores derived from complex measures frequently involve a measure of discretion, which might be subtly influenced by prior knowledge of drug regimen.

Binder and Doddabela's (1976) double-blind cross-over study constituted a stronger test of piracetam's efficacy. They repeated Binder's (1974) findings, although the tests used were mostly not directly comparable. One of the measures used however was a "guessing test" by which they attempted to identify whichever regimen was being applied to each subject, and this test yielded highly significant results ($p < ,01$). These guesses were based on the performance of subjects in therapeutic group situations, but nevertheless this points to some observable, though not necessarily measurable, result of piracetam treatment.

This result must militate against the efficacy of the double-blind methodology however, and consequently the likelihood of bias in test scoring is very strong.

The distinction made by these authors between simple "stimulus-response" functions and more complex ones, for which piracetam is claimed to show differential efficacies, does not appear to be a sound one, as within the former category they included a mirror drawing task, and an enumeration task, both of which do not conform to a "stimulus-response" description.

In the present study, no differences, even in trends, were seen between simple and complex functions' responses to piracetam treatment. In particular, measures reflecting accuracy rather than speed, did not respond positively to piracetam as might have been expected from reading certain piracetam studies (e.g. Binder 1974; Binder and Doddabela, 1976; Demay and Bande, 1980).

It thus seems inadvisable to dismiss non-significant results in this

fashion, and to accept the test scores as a unified group, some of which attain significance while others do not. In any event, the authors may be faulted for contending in summing up that piracetam raised the general level of all performances, while not relating this to their failure to attain significance on half their tests.

While it is not possible (due to insufficient details being reported) to determine to what extent these samples were comparable, it can be seen that several factors can account for the divergent findings between those of Binder (1974) and Binder and Doddabela (1976) on one hand, and the present study on the other, even were the issue of abstinence to be glossed over. The present study has the strongest design, the lessened degree of contact with subjects protecting the double-blind procedure.

The study, and the conclusions of Binder (1974) have been faulted on several grounds, and though the Binder and Doddabela (1976) study was much sounder, the double-blind procedure was betrayed and hence its results should be treated as contaminated. In both cases, the authors appear to have exceeded the claims of their results in their strong endorsement of piracetam's efficacy. It must be emphasized, however, that there exists the possibility that during the first few weeks after detoxification there might exist an interaction of the effects of piracetam and that of absence of alcohol, which might lead to accelerated recovery. If very large, this could just conceivably account for Binder and Doddabela's (1976) positive findings, but on balance these still appear suspect. The possibility of such interaction in the present study is however practically nil, as a minimum period of 3 months' abstinence from problem drinking was required prior to entry into this trial. By such a time, recovery of equilibrium is complete, and the only changes should be extremely small protracted ones related to long-term, not acute, deficits.

It thus appears that in piracetam studies concerning chronic alcoholism the findings of Binder (1974) and Binder and Doddabela (1976) can largely be dismissed. The failure to find any significant effects due

to treatments, or even trends, other than expected chance effects, in so large a number of analyses, appears to argue most forcibly that treatment with piracetam was totally without measurable effects.

6.5 THE RELATIONSHIP OF THESE FINDINGS TO THE GENERAL LITERATURE ON PIRACETAM

Consideration of the internal validity of this study did not reveal any factors which might have given rise to erroneous conclusions, and in consequence it must be accepted that in the present sample of abstinent alcoholics, piracetam did not exert any effects differing from those of the placebo.

However, being the first study of its kind, this study must be regarded as exploratory, and its conclusions should be checked against those of replication studies. It is normal practice to treat such conclusions as tentative, as it is conceivable, for instance, that the use of a non-random sample might have resulted in unknown biases.

On the other hand, though, the uniform nature of the large number of results argues most strongly against a contention of sampling bias. It is inconceivable, bearing in mind the sample size and the repeated measures design combined to ensure detection of relatively small differences, that the alcoholic population should vary so widely on morphologically-based functional impairments that one non-random sample should reflect no differences between placebo and piracetam on an extensive range of 31 measures whilst another non-random sample might do so. On such sensitive analyses, differences would have to be found on the majority of measures, and plausible reasons would have to be offered for those results failing to attain significance, before a conclusion supporting differences between placebo and piracetam could be accepted. The obtained results differ so much from this that it is highly improbable that this could be the result of sampling bias. The conclusion has to be accepted that the results unambiguously

and incontestably showed that piracetam and placebo treatments did not differ. Bearing in mind the strength with which this conclusion is supported, it is difficult to be tentative in this regard. In as sound a design, this result is unlikely to be contradicted in replication.

This finding runs counter to numerous others which support the contention that piracetam yields beneficial effects on functional capacities, in non-alcoholic as well as in alcoholic samples.

Negative findings have been reported frequently, however. In a review of controlled and randomized double-blind studies conducted in elderly populations, Bogaert (1979) found that of 12 such studies, 6 returned negative results. Bogaert went further, scrutinizing the remaining 6 studies, and concluded that the magnitude of improvements observed in these did not justify the strength of the claims made for piracetam's efficacy, based on these changes.

It is important to note that Bogaert (1979) chose to ignore all drug studies which did not conform to the randomized double-blind design, as all other designs could be faulted. In spite of this rigorous selection, however, he still found ample examples of what might be termed "errors of enthusiasm" in interpretation of results. It can only be presumed that if such willingness can be found in rigorous trials, its potential for biasing less controlled studies is immense.

Thus it appears wise to examine all drug studies not utilizing randomized double-blind designs with care. Examining the literature on piracetam's effects in the normal population, reports of the use of double-blind cross-over designs are made by Lagergren and Levander (1974), Wedl and Suchenwirth (1977) and Demay and Bande (1980), but none of these explicitly mentions using randomized allocation to groups, in fact it seems probable that Demay and Bande (1980) used a single group repeated measures design (the authors do not make this matter clear). If so, it appears piracetam treatment was given last.

Assuming increasing longitudinal learning effects, while acknowledging that these are indistinguishable from the treatment effects, it is evident that in the absence of real differences between treatment effects, there will nonetheless appear to be differences, which in reality represent differing degrees of learning and carryover effects. In the present case, this would appear to indicate that piracetam treatment resulted in superior performance to that resulting from the prior placebo treatment, but this would be a spurious conclusion.

Lagergren and Levander (1974) were more guarded in concluding that piracetam had "some protective effect" or "some cortical arousing effect" on their pacemaker subjects. However, no baseline measurements were taken, and as the differences resulting from the differing treatments are so small, it might be contended that the results obtained are the results of random sampling variation. Certainly, the conclusions drawn were supported by only 2 of the 4 tests applied, which weakens them somewhat. Wedl and Suchenwirth (1977) appear open to the same charge, reporting 5 significant results while ignoring another 16 which failed to attain significance. As several tests used in this study are not known here, it is not possible to assess how objective the scoring may be. The major criticism concerns the questioning of subjects as to whether they received active medication or placebo. As the trial lasted 10 days (2 periods of 5 days each) even were this question to be asked at the very end of testing, since the trial lasted a total of 28 days it is possible the study could have been confounded by communication about this matter from early finishers to later starters. As the subjects were all nursing students, it is very possible they had sufficient opportunity to do so. In addition, nursing students would be aware of the major role placebo treatment plays in drug trials, and hence even without confirmation from early finishers their "blindness" must be suspect.

Of other studies in the normal population, that of Dimond (1975) is open to many forms of contamination and bias. While reporting significant improvements in verbal learning under piracetam treatment,

Dimond provided too few details of methodology, statistical treatments and directionality of his hypothesis to support any criticisms of his research. However, he used psychology students as subjects. These should have similar knowledge of the use of placebos to that possessed by nursing students, and thus again the possibility of contamination via reduced placebo efficiency has to be considered. Also, Dimond reported one statistically significant result, but mentioned conducting studies on other aspects of learning, not mentioning the number of these. It is thus again possible that an isolated positive finding has been misinterpreted as showing real drug effects when it reflects chance factors, the majority of negative findings simply being ignored.

It can be seen, then, that much of the literature supporting the claims of piracetam may be faulted on procedural and methodological grounds. Of much of the rest of such literature no specific criticism is possible due to insufficient details being supplied, but the possibility exists that similar criticisms to those given above might well apply equally to these, were all relevant details known. It appears that the type of criticism levelled by Bogaert (1979), namely that researchers are overkeen in these drug trials to interpret positive findings from their data, minimizing negative results, can be extended from those studies on elderly subjects reviewed by Bogaert to those of Lagergren and Levander (1974), Dimond (1975), Wedl and Suchenwirth (1977) and Demay and Bande (1980). Consequently, much of the literature favourable to piracetam is open to dispute.

It would however be arrogant to assert that the findings of the present study are sufficient to negate all this previous work. Despite the uniformity of the results obtained, which appears to allow only one, unambiguous interpretation, to wit, that piracetam was no more beneficial than placebo, and despite this conclusion being drawn from a study of great internal validity and sensitivity to small differences, the fact, that this study had unique characteristics in terms of the subject selection criteria used and the particular aspect

of chronic alcoholism investigated, namely that of abstinence from problem drinking for upwards of three months, forces one to require replication of this study before unreservedly accepting its findings. A larger sample might make for detection of even smaller differences, for instance, but even were such differences to be found, it would have to be asked whether such small differences were of practical significance.

Replication, albeit almost certainly requiring the use of another non-random sample, is desirable because all subjects used in this study were solicited volunteers, drawn from a single institution and thus constituting a selected non-random sample; because of the inevitable number and diversity of uncontrolled variables in the lives of out-patients; and because of the difficulties inherent in accurately ascertaining the degree of non-compliance with the treatment regimen, in terms of pill consumption. On this last point, it was hoped that by using a selection criterion of patient "reliability" that difficulties with non-compliance would be minimized, and that random allocation to groups would spread undetected non-compliance across the two groups. However, there was an extensive failure on the part of subjects to return unused drug supplies as requested, and hence in such cases it was not possible to accurately assess compliance, aside from obtaining assurances that most of the supplies had been consumed. Even in those cases of returned drug supplies, a researcher cannot be sure that the missing pills have been consumed rather than disposed of in some other way. It can only be hoped that the highly motivated behaviour associated with volunteer subjects mitigates against extensive non-compliance. The only exclusion criterion which could be applied relating to drug use was therefore related exclusively to excessive drug returns. This provides the strongest grounds for requiring replication of this study, as extensive non-compliance, had it occurred, could have diluted differences between treatments to non-significant levels. This could then have given rise to the results seen in this study.

It is not believed that this occurred, however, as very large dosages

(4,8gm/day) were used, which were double the size of normal long term dosages. Thus, were the odd dose missed, extensive effects from the previous dose could still be expected to be present. In addition, the combination of characteristics associated with volunteer subjects, and the "reliability" criterion applied in selecting subjects should have combined to militate against non-compliance. Finally, examination of the cell mean profile graphs fails to reveal more than a handful of graphs which might be interpreted as showing "diluted" differences between treatments. Many graphs show approximately parallel lines over the entire trial period, which can not fit the above interpretation. Ignoring the non-directional hypothesis used in this study, and accepting that according to the literature, piracetam should have improved performance, it can be seen that only Figures 4, 6, 8, 11 and 29 could conceivably lend support to this idea, and only weakly.

Overall, then, it is believed that although this study should be repeated, it is most improbable that differing conclusions could result, and in all probability the results obtained would echo those obtained in the present study.

6.6 IMPLICATIONS FOR FUTURE RESEARCH ON PIRACETAM

Criticisms levelled at much of the existing research findings on piracetam have made it plain that rigorous design is an absolute necessity in such research, as without it the relationships between drug treatments and the dependent variables become obscured and contaminated. Placebo-controlled double-blind studies offer the purest test of such relationships, but such designs must be two group designs. It appears that in some cases "double-blind" studies as they are described are nothing other than single group repeated measures designs, and in these cases sequence effects play a major role, better performances being yielded at each successive assessment. These studies, then, do not permit accurate evaluation of the effects of preceding treatments, and can give rise to totally misleading

conclusions.

The addition of a cross-over to placebo controlled, double-blind studies adds to their strength by reducing the impact of intersubject differences, each subject acting as his own control in both treatment conditions. As random sampling will continue to be the exception in drug trials using clinical populations, randomized assignment to groups is the best guarantee of the equality of groups, but the representativeness of the samples drawn will always be open to question.

It is not advisable that sample sizes be increased, though in theory this would make it easier to attain significant results. Not only would sample sizes have to increase enormously to achieve minor gains in sensitivity, but the question of practical significance of such small differences would be raised. Consideration could be given to increasing the initial sample size in a replication of this study, however, with a view to eliminating those subjects who do not return their unused drug supplies. As pointed out earlier, this is no guarantee that unreturned pills, originally issued to those subjects who do return some pills, have been consumed. It would however provide a slightly more stringent control on non-compliance, though it is doubtful whether the gains would outweigh the additional costs and work involved.

A better solution to this non-compliance problem involves the use of blood assays on a regular basis. With out-patients however this would be difficult to arrange, as their contact with institutions though regular, frequently is separated by long intervals. Many experience great difficulty, arising out of their life situations, in reaching such institutions, through, for instance, loss of a driving licence, or the need to disguise from an employer the fact that they receive treatment for alcoholism. Blood samples could be taken at the times of assessment, but this would not guarantee that the drug had been consumed regularly for the treatment period, merely that it had been consumed within the previous two days. In addition, this would

necessitate the addition of an inert traceable element to the placebo, as it would be as important to check on this consumption.

It is apparent that there are numerous difficulties inherent in running a long term drug trial involving alcoholic out-patients. More control can be exerted in an in-patient situation, but the possibilities of contamination are so much greater. Also, subjects in an in-patient situation do not remain so for the duration of this type of trial in this country, and even were this so, the necessity of stabilizing the physiological and functional parameters before beginning to investigate this drug's effects on long term deficits would probably necessitate an even longer in-patient treatment. Were an in-patient study possible, it would not be necessary to insist on a selection criterion of "reliability" to guard against a high drop-out rate. However, it would be necessary to induce patients to participate without motivating them too strongly to find the "correct" way to respond (e.g. to gain early discharge from hospital), and it would be very important to minimize demand effects.

It is desirable that researchers minimize contact with subjects, so as not to jeopardize the double-blind, and refrain from guessing tests for the same reason, and because this might influence scoring. Where there is a likelihood of contact between subjects, when some finish well before others, post-trial questionnaires should not be administered if the questions separately or in combination lend themselves to the suggestion of a placebo treatment having been given. Scoring should be completed before breaking of any protocols, and should only occur after termination of the trial, to prevent early scores influencing later ones.

The above recommendations should be considered in planning future piracetam trials involving alcoholics, though many of these suggestions could apply to research in other fields.

Should sound replications of the present study repeat these findings,

the indications for the continued use of piracetam in several fields, not merely in that of alcoholism, would be very poor. Most studies supporting piracetam's usefulness in chronic alcoholism, the psycho-organic syndrome of aging and in the normal population may be criticised on methodological grounds, and it is doubtful that collectively their conclusions could gainsay opposed findings from a few well designed studies.

There are several reasons why replication of this study's findings would hold implications for piracetam's use in other fields of study. Once the acute effects of alcohol toxicity and of withdrawal have been removed, impaired brain cells quickly re-attain healthy status. Thus there should be no differences in the action of piracetam on cell metabolism in the brains of alcoholics and non-alcoholics, provided the alcoholics have passed through the withdrawal phase. The two populations may differ in the extent of the effects piracetam exerts on them, but they should nonetheless appear to be similar. Though these populations will differ in the amounts of healthy cell matter in their brains, it cannot be stated with certainty that the superiority in this regard of non-alcoholics will result in their showing a better response to piracetam, based simply on their larger capacity to process piracetam. The relationship between changes at a physiological level and those at a functional level is complex and little understood, and it does not follow that a change at the physiological level must lead to an observable change at a functional level (Lyons, 1965).

Thus, conclusions drawn from sound studies of piracetam's effects on alcoholics should bear some resemblance to its effects on the normal population. If the research on alcoholism finds itself yielding extreme results which are irreconcilably at odds with those obtained in studies of the normal population, the difference must be accounted for. Opposing sound studies against questionable ones, one must inevitably conclude that the results of the alcoholism studies are more

likely to reflect reality, and the conclusions drawn from studies in the normal population must be discarded and those of the alcoholism studies extended in a qualified form to cover the normal population until well controlled appropriately designed studies of piracetam's efficacy in the normal population are completed. It is doubtful that a sound piracetam trial in the normal population would arrive at findings much different from those obtained in the present study, however.

The literature surveyed in the Introduction to this study clearly indicated that chronic alcoholics exhibit a clinical picture of advanced cortical atrophy, particularly in the frontal lobes, but extending somewhat to the temporal and parietal lobes, with a common incidence of ventricular enlargement. Memory, attention and concentration, complex thought and general response speed all deteriorate (Lezak, 1976). Kish and Cheyne (1969) noted that relative to non-alcoholics, alcoholics presented a clinical picture similar to that of advanced aging. The most striking similarity between alcoholics and the aged lies in the marked diffuse, symmetrical cortical atrophy present. In the aged, this is the cumulative result of the normal loss of brain cells over many years, but alcoholics achieve a similar status at much younger ages due to the toxic effects of alcohol, and to an unmeasurable but probably lesser extent, to minor head injuries which are fairly common among alcoholics.

This clinical similarity suggests that alcoholics and the aged are more similar than are alcoholics and normal subjects. To some extent they may differ in that the aged's cell loss is part of a markedly progressive condition in which poor circulation results in inefficient oxygenation of brain cells, and therefore cell metabolism might not be as efficient as could be expected in abstinent alcoholics and in normal subjects. However the findings of Herrschaft (1979) on the effects of piracetam in rectifying circulatory imbalances means that the effectiveness of piracetam treatment should be the same in the aged as in alcoholics and normal subjects.

Support via replication for this study's findings would therefore have to be related to findings in the area of the psycho-organic syndrome of aging. Negative findings in alcoholism studies would seem to imply that piracetam should not prove effective in the treatment of the effects of advanced aging either. As it happens, Bogaert (1979) in reviewing the most rigorous trials in this area concluded that half the studies had found no effects of piracetam, while the remainder had reported weak positive results which had subsequently been over-interpreted. Overall then the findings of the present study are similar to those found in the area of advanced aging, although the latter studies must be regarded as slightly more favourable to piracetam, in that the weak positive findings can not be dismissed totally without further close scrutiny of these results. It can be stated however that piracetam's effects in this population are at best extremely weak and unlikely to represent any worthwhile clinical or functional improvement.

It can therefore be seen that the findings of the present study undermine the conclusions drawn from studies of piracetam's efficacy in the normal population and in the population afflicted by the effects of advanced aging, and replication of these findings, resulting from completion of a well designed and executed trial, would make it extremely difficult to maintain the standpoint that piracetam can be of benefit to subjects of fairly stable functional status. This would not however necessarily hold any implications for piracetam's use in acute conditions such as drug overdosages, cerebral trauma and post-anaesthetic recovery, which seem more closely related to piracetam's demonstrated activity in cell metabolism. In these cases piracetam's claimed protective effect might well reduce cerebral cell damage and death, resulting in more rapid and positive resolution of these acute states. It appears more likely that piracetam might be of clinical benefit in these areas, and this is where further research might be most usefully directed.

REFERENCES:

Acker, W. Objective psychological changes in alcoholics after the withdrawal of alcohol. British Medical Journal, 1982, 38, 95-98.

Acker, W., Aps, E.J., Majumdar, S.K., Shaws, G.K. and Thomson, A.D. The relationship between brain and liver damage in chronic alcoholic patients. Journal of Neurology, Neurosurgery and Psychiatry, 1982, 45, 984-987.

Adams, K.M., Grant, I. and Reed, R. Neuropsychology in alcoholic men in their late thirties: one year follow-up. American Journal of Psychiatry, 1980, 137 (8), 928-931.

Almeida Vargas, M. Therapeutic effects of piracetam in the acute alcohol withdrawal syndrome. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 173-182.

Anastasi, A. Psychological testing. London: MacMillan, 1968.

Bente, D. Vigilance: psychophysiological aspects. Paper read at the 83rd Meeting of the German Society of Internal Medicine, 1977, 945-952.

Berglund, M. and Ingvar, D.H. Cerebral bloodflow and its regional distribution in alcoholism and in Korsakoffs psychosis. Journal of Studies on Alcohol, 1976, 37, 586-597.

Bergman, H., Borg, S., Hindmarsh, T., Ideström, C.M., and Mutzell, S. Computed tomography of the brain, clinical examination and neuropsychological assessment of a random sample of men from the general population. Acta Psychiatrica Scandanovica, Supplement, 1980(a), 286, 47-56.

Bergman, H., Borg, S., Hindmarsh, T., Ideström, C.M., and Mutzell, S. Computed tomography of the brain and neuropsychological assessment of male alcoholic patients and a random sample from the

general male population. Acta Psychiatrica Scandanavica, Supplement, 1980(b), 286, 77-88.

Binder, S. The effect of the nootropic agent piracetam on the cortical efficiency of chronic alcoholics. Munchner Medizinische Wöchenschrift, 1974, 116, 2127-2130.

Binder, S. and Doddabela, P. The effect of piracetam upon the mental performance in chronic alcoholics. Med. Klin., 1976, 71, 711-716.

Bogaert, M. Piracetam. In: G. Tognoni and S. Garattini (Eds.). Drug treatment and prevention in cerebrovascular disorders. Elsevier: North-Holland and Biomedical Press, 1979.

Bonifaci, J.F., Ferran,C. and Laborit, H. Piracetam promotes protein synthesis. Paper read at the International Symposium on Nootropic Drugs, Paris, 1982, 131-137.

Burnotte,R.E., Gobert, J.G. and Temmerman, J.J. Piracetam induced modifications of the brain polyribosome pattern in aging rats. Biochemical Pharmacology, 1973, 22, 811-814.

Buschke, H. Selective reminding for analysis of memory and learning. Journal of Verbal Learning and Verbal Behaviour, 1973. 12, 543-550.

Buschke, H and Fuld, P.A. Evaluating storage, retention and retrieval in disordered memory and learning. Neurology, 1974, 24, 1019-1025.

Caird, W.K., Sanderson, R.E. and Inglis,J. Cross validation of a learning test for use with elderly psychiatric patients. Journal of Mental Science, 1962, 108, 368-370.

Cala, L.A. and Mastaglia, F.L. Computerized axial tomography in the detection of brain damage. Medical Journal of Australia, 1980,2, 193-198.

Cala,L.A., Jones,B., Mastaglia,F.L. and Wiley,B. Brain atrophy and intellectual impairment in heavy drinkers - a clinical, psychometric and computerized tomographic study. Australian and New Zealand Journal of Medicine, 1978, 8, 147-153.

Cala, L.A., Jones,B., Wiley,B. and Mastaglia, F.L. A computerized axial tomography (CAT) study of alcohol-induced cerebral atrophy - in conjunction with other correlates. Acta Psychiatrica Scandanavica, Supplement, 1980, 286, 31-40.

Calliauw, L. and Marchau, M. Clinical trial of piracetam in disorders of consciousness due to head injury. Acta Anaesthesiologica Belgica, 1975, 26, 51-60.

Carlen, P.L. and Wilkinson, D.A. Alcoholic brain damage and reversible deficits. Acta Psychiatrica Scandanavica, Supplement, 1980, 268, 103-118.

Carlen, P.L., Wortzman, G., Holgate, R.C., Wilkinson, D.A. and Rankin, J.G. Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomographic scans. Science, 1978, 200, 1076-1078.

Caro Mendevil, M.A. Clinical work in patients with a senile psycho-organic syndrome, using the drug piracetam. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 31-47.

Carlsson, C., Claeson, L.E., Karlsson, K.I. and Petterson, L.E. Clinical, psychometric and radiological signs of brain damage in chronic alcoholism. Acta Neurologica Scandanavica, 1979, 60, 85-92.

Castellanos, V. and Velasco Suarez, M. The use of piracetam in the psycho-organic syndrome of senility. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 49-52.

Chelune, G.J. A re-examination of the relationship between the Luria-Nebraska and Halstead-Reitan Batteries: overlap with the WAIS. Journal of Consulting and Clinical Psychology, 1982, 50, 578-580.

Chouinard, G., Annable, L., Olivier, M., Fontaine, F., and Ross-Chouinard, A. Psychotropic and neuropsychologic effects of piracetam in geriatric patients: a controlled study: preliminary report. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 23-30.

Clarke, J. and Haughton, H. A study of intellectual impairment and recovery rates in heavy drinkers in Ireland. British Journal of Psychiatry, 1975, 126, 178-184.

Costa, L.D., Vaughan, H.G., Levita, E., and Farber, N. Purdue pegboard as a predictor of the presence and laterality of cerebral lesions. Journal of Consulting Psychology, 1963, 27, 133-137.

Cutting, J. Specific psychological deficits in alcoholism. British Journal of Psychiatry, 1978, 133, 119-122.

Demay, F. and Bande, J. The effect of piracetam on volunteers in a low pressure tank. Journal of International Medical Research, 1980, 8, 90-94.

Dimond, S.J. Use of a nootropic substance to increase the capacity for verbal learning and memory in normal man. Paper read at the 3rd Congress of Psychosomatic Medicine, Rome, 1975, 107-110.

Eckhardt, M.J., Ryback, R.S. and Paulter, C.P. Neuropsychological deficits in alcoholic men in their mid-thirties. American Journal of Psychiatry, 1980, 137, 932-936.

Fox, J.H., Ramsey, R.G., Huckman, M.S. and Proske, A.E. Cerebral ventricular enlargement. Chronic alcoholics examined by computed tomography. Journal of the American Medical Association, 1976, 236, 365-368.

FitzHugh, L.C., FitzHugh, K.B. and Reitan, R.M. Adaptive abilities and intellectual functioning in hospitalized alcoholics. Quarterly Journal of Studies on Alcohol, 1960, 21, 414-423.

FitzHugh, L.C., FitzHugh, K.B. and Reitan, R.M. Adaptive abilities and intellectual functioning of hospitalized chronic alcoholics: further considerations. Quarterly Journal of Studies on Alcohol, 1965, 26, 402-411.

Garay, O. and Castro, J.C. Effects of piracetam in patients with decreased vision due to vascular disturbances associated with arteriosclerosis. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 327-331.

Gilbert, L. Deciding upon a sample size. Unpublished Honours Research Methodology Notes, University of Cape Town, 1977a.

Gilbert, L. Issues and assumptions in the anova. Unpublished Honours Research Methodology Notes, University of Cape Town, 1977b.

Gilbert, L. Repeated measures in the two-way anova. Unpublished Honours Research Methodology Notes, University of Cape Town, 1977c.

Gobert, J.G. and Baltes, E.L. Availability and plasma clearance of piracetam in man. Il Farmaco, 1977, 32, 84-91.

Graff-Radford, N.R., Heaton, R.K., Earnest, M.P. and Rudikoff, J.C. Brain atrophy and neuropsychological impairment in young alcoholics. Journal of Studies on Alcohol, 1982, 43, 459-468.

Grant, I., Adams, K. and Reed, R. Normal neuropsychological abilities of alcoholic men in their late thirties. American Journal of Psychiatry, 1977, 136, 1263-1269.

Griffin, P.T. and Heffernan, A. Digit Span, forward and backward: separate and unequal components of the WAIS digit span. Perceptual and Motor Skills, 1983, 56, 335-338.

Guirgea, C. The "nootropic" approach to the pharmacology of the integrative activity of the brain. Conditional Reflex, 1973, 8, 108-115.

Guirgea, C. and Salama, M. Nootropic drugs. Progressive Neuropsychopharmacology, 1977, 1, 235-247.

Guthrie, A. and Elliot, W.A. The nature and reversibility of cerebral impairment in alcoholism. Journal of Studies on Alcohol, 1980, 41, 147-155.

Hamilton, M. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry, 1960, 23, 56-62.

Harper, C. Neuropathology of brain damage caused by alcohol. Medical Journal of Australia, 1982, 2, 277-282.

Harper, C. and Plumbergs, P.C. Brain weights in alcoholics. Journal of Neurology, Neurosurgery and Psychiatry, 1982,45, 838-840.

Heinitz, M. Therapeutic perspectives of piracetam in cerebral insufficiency. Fortschrifte der Medizin, 1975, 6, 3-14.

Herrschaft, H. The efficacy and course of action of vasoactive and metabolically active substances on regional cerebral blood flow in patients with acute or sub-chronic brain ischemia. Paper read at the International Symposium on Nootropic Drugs, Rio de Janiero, 1979, 63-77.

Hindmarch, I. Psychomotor function and psychoactive drugs. British

Journal of Clinical Pharmacology, 1980, 10, 189-209.

Inglis, J. A paired associate learning test for use with elderly psychiatric patients. Journal of Mental Science, 1959, 105, 440-443.

Isaksson, A., Lagergren, K. and Wennberg, A. Interaction between heart rate and spectral parameters of the EEG. A pilot study on piracetam treated patients with cardiac pacemakers. Proceedings of the 2nd Symposium of the study group for EEG Methodology, Jongny sur Vevey, 1975, 149-157.

Jones, B.M. Verbal and spatial intelligence in short and long term alcoholics. Journal of Nervous and Mental Disease, 1971, 153, 292-297.

Jones, B.M. and Parsons, O.A. Impaired abstracting ability in chronic alcoholics. Archives of General Psychiatry, 1971, 24, 171-175.

Kabes, J., Erban, L., Dostal, T., Hanzlicek, L., and Skondia, V. Clinical and biochemical action of piracetam in drug resistant depression. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 277-283.

Kish, G.B. and Cheyne, T.M. Impaired abilities in alcoholism measured by the General Aptitude Test Battery. Quarterly Journal of Studies on Alcohol, 1969, 30, 384-388.

Kleinknecht, R.A. and Goldstein, S.G. Neuropsychological deficits associated with alcoholism: A review and discussion. Quarterly Journal of Studies on Alcohol, 1972, 33, 990-1019.

Knott and Beard. Summary of study in acute alcohol withdrawal. Unpublished U.C.B. file material.

Lagergren, K. and Levander, S. A double-blind study on the effects of piracetam upon perceptual and psychomotor performance at varied heart rates in patients treated with artificial pacemakers. Psychopharmacologia, 1974, 39, 97-104.

Lee, K., Möller, L., Hardt, F., Hanbeck, A. and Jensen, E. Alcohol induced brain damage and liver damage in young·males. The Lancet, October 13th, 1979, 759-761.

Lee, K., Jensen, E. and Bech, P. Neuropsychological and computerized tomographic evaluations of young alcoholics. British Journal of Psychiatry, 1982, 141, 282-285.

Lezak, M.D. Neuropsychological assessment. New York: Oxford University Press, 1976.

Lishman, W.A. Cerebral disorder in alcoholism. Brain, 1981, 104, 1-20.

Long, J.A. and McLachlan, J.F. Abstract reasoning and perceptual-motor efficiency in alcoholics. Impairment and reversibility. Quarterly Journal of Studies on Alcohol, 1974, 35, 1220-1229.

Lusins, J. and Zimberg, S. Alcoholism and cerebral atrophy: a study of 50 patients with CT scan and psychological testing. Alcoholism, 1980, 4, 406-411 (Abstract)

Lynch, M.J.G. Brain lesions in chronic alcoholics. Archives of Pathology, 1960, 69, 342-353.

Lyons, J. A Primer of experimental psychology, New York: Harper and Row, 1965.

McGhie, A. Pathology of attention. Harmondsworth: Penguin, 1969.

McLachlan, J.F.C. and Levinson, T. Improvement in WAIS Block Design Performance as a function of recovery from alcoholism. Journal of Clinical Psychology, 1974, 30, 65-66.

Maloney, M.P.and Ward, M.P. Psychological assessment: a conceptual approach. New York: Oxford University Press, 1976.

Marks, N.S. Controlled clinical trial of piracetam in the treatment of the alcoholic withdrawal phase. Acta Therapeutica, 1977, 3, 181-190.

Matarazzo, J.D. Wechsler's measurement and appraisal of adult intelligence. Baltimore: Williams and Wilkins, 1972.

Melges, F.T., Tinklenberg, J.R., Hollister, L.E. and Gillespie, H.K. Marihuana and temporal disintegration. Science, 1970, 168, 1118-1120.

Miller, W.R. and Orr, J. Nature and sequence of neuropsychological deficits in alcoholics. Journal of Studies on Alcohol, 1980, 41, 325-337.

Mindus, P., Cronholm, B., Levander, S.E. and Schalling, P. Piracetam induced improvement of mental performance: a controlled study on normally aging individuals. Acta Psychiatrica Scandanavica, 1976, 54, 150-160.

Nalbanian, R.M. and Henry, R.L. An overview of desickling and other effects of piracetam on blood. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 185-194.

National Institute of Personnel Research. The South African Wechsler Adult Intelligence Test. Johannesburg: Author, 1969.

Nelson, H.E. A modified card sorting test sensitive to frontal lobe defects. Cortex, 1976, 12, 313-324.

Oblowitz, H. The effects of clobazam, lorazepam and placebo on patients psychomotor performance, memory and anxiety. Unpublished Masters Thesis, University of Cape Town, 1982.

O 'Leary, M.R., Donovan, D.M., Chaney, E.F., Walker, R.D. and Schau,E.J. Application of discriminant analysis to level of performance of alcoholics and non-alcoholics on Wechsler-Bellevue and Halstead-Reitan sub-tests. Journal of Clinical Psychology, 1979, 35, 204-208.

Page, R.D. and Linden, J.D. "Reversible" organic brain syndrome in alcoholics. A psychometric evaluation. Quarterly Journal of Studies on Alcohol, 1974, 35, 98-107.

Page, R.D. and Schaub, L.H. Alcoholic consumption and cognitive function in social drinkers. Journal of Studies on Alcohol, 1977, 38, 1224-1232.

Parker, E.S. and Noble, E.P. Alcohol and the aging process in social drinkers. Journal of Studies on Alcohol, 1980, 41, 170-178.

Pendleton, M.G. and Heaton, R.K. A comparison of the Wisconsin Card Sorting Test and the Category Test. Journal of Clinical Psychology, 1982, 38, 392-396.

Petty, L. Summary of study in acute alcohol withdrawal. Unpublished UCB file material.

Richardson, A.E. and Bereen, F.J. Effect of piracetam on level of consciousness. The Lancet, November 26, 1977, 1110-1111.

Rivas Vidal, V. Advantage of piracetam in post-anaesthetic recovery. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 121-128.

Rix, K.J.B. Alcohol problems. Bristol: Wright, 1983.

Ron, M.A. Brain damage in chronic alcoholism: a neuropathological, neuroradiological and psychological review. Psychological Medicine, 1977, 7, 103-112.

Ron, M.A., Acker, W. and Lishman, W.A. Morphological abnormalities in the brains of chronic alcoholics. A clinical, psychological and computerized axial tomographic study. Acta Psychiatrica Scandanavica, Supplement, 1980, 286, 41-46.

Ron, M.A. The alcoholic brain: C.T. scan and psychological findings. Psychological Medicine, Supplement 3, 1982, 1-33.

Ryan, C. Learning and memory deficits in alcoholics. Journal of Studies on Alcohol, 1980, 41, 437-447.

Samayoa de Leon, R. Piracetam: clinical use in 50 high risk patients. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 113-119.

Sarason, I.G. and Sarason, B.R. Abnormal psychology. Englewood Cliffs: Prentice-Hall, 1980.

Schau, E.J., O 'Leary, M.R. and Chaney, E.F. Reversibility of cognitive deficits in alcoholics. Journal of Studies on Alcohol, 1980, 41, 733-740.

Schvartsman, S. Piracetam in the treatment of children with severe psychotropic drug poisoning. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 169-172.

Skondia, V. Evaluation of piracetam in senile psycho-organic syndromes, (cerebrovascular pathology). Paper read at the International Symposium on Nootropic Drugs, Paris, 1982, 184-191.

Smythies, J.R. Brain mechanisms and behaviour. Oxford: Blackwell, 1966.

Suchenwirth, R.M. Six years use of piracetam in Germany: A literature review. Paper read at the International Symposium on

Nootropic Drugs, Rio de Janeiro, 1979, 53-60.

Talland, G.A. Alcoholism and reaction time. Quarterly Journal of Studies on Alcohol, 1963, 24, 610-621.

Tarter, R.E. An analysis of cognitive deficits in chronic alcoholics. Journal of Nervous and Mental Disease, 1973, 157, 138-147.

Tarter, R.E. and Parsons, O.A. Conceptual shifting in chronic alcoholics. Journal of Abnormal Psychology, 1971, 77, 71-75.

Teichner, W.H. and Krebs, M.J. Laws of visual choice reaction time. Psychological Review, 1974, 81, 75-98.

Thorndyke, E.L. and Lorge, I. The teacher's word book of 30,000 words. New York: Columbus University, 1944.

Tiffin, J. Purdue pegboard examiner manual. Chicago: Science Research Associates, 1968.

U.C.B. Nootropil. Brussels: Author, 1980.

Ulbricht, B. On the clinical use of piracetam in chronic alcoholism and it's complications, delirium and pre-delirium. Med. Welt, 1976, 27. (U.C.B. translation).

Vaughan, H.G. and Costa, L.D. Performance of patients with lateralized cerebral lesions: sensory and motor tests. Journal of Nervous and Mental Disease, 1962, 134, 237-243.

Volavka, J., Simeon, J., Simeon, S., Dong Cho. EEG effects of piracetam in children with learning disorders. Paper read at the International Symposium on Nootropic Drugs, Rio de Janeiro, 1979, 89-94.

Von Gall, M., Becker, H., Artman, H., Lerch, G. and Nemeth, N. Results of computer tomography in chronic alcoholics. Neuroradiology, 1978, 16, 329-331.

Wechsler, D. The measurement of adult intelligence. London: Bailliere, Tindall and Cox, 1958.

Wedl, W. and Suchenwirth, R.M.A. Effects of the GABA derivative piracetam: a double-blind study in healthy volunteers. Der Nervenartz, 1977, 48, 58-60.

Wilkinson, D.A. and Carlen, P.L. Neuropsychological and neurological assessment of alcoholism. Journal of Studies on Alcohol, 1980, 41, 129-139.

Zelozowiki, R., Goldin, C.J., Graber, B., Blose, I.L., Block, S., Moses, J.A., Zatz, L.M., Stahl, S.M., Osmon, D.C. and Pfefferbaum, A. Relationships of cerebral ventricular size to alcoholics performance on the Luria-Nebraska neuropsychological battery. Journal of Studies on Alcohol, 1981, 42, 749-756.

APPENDICES

17. Approximate Length of Drinking HIstory, Serious Medical Conditions and Current Medication of Full Sample

18. The Influence of Psychotropic Drugs on Results Obtained - Statistical evaluations of differences between groups

19. Issues relating to Sample Size

20. Raw Data

APPENDIX 1

REACTION TIMER, TECHNICAL DETAILS

This apparatus consisted of the timer itself and an impulse generator which connected into it. Both were electrically operated.

The impulse generator was a motor-driven device which rotated two discs in the horizontal plane. The uppermost disc had two sets of pins set into its perimeter, one on the uppermost and one on the lower surface, while the second disc carried a single set of pins on its upper surface.

As the discs rotated, each set of pins triggered its respective microswitch, which then initiated onset of the respective visual stimulus (in each case a different coloured light). Pins were arranged in an order such that when the discs rotated simultaneously, at any one time only one impulse would be triggered, and that the intervals between impulses would be four seconds. This device had its own on/off switch to commence testing, and an automatic cut-out at the end of practice and the end of testing.

The reaction timer was a portable device made specially for this trial by Mr. A. Reynolds, (technician, Department of Psychology, UCT). It bears no technical relation to other reaction timers. It was constructed in such a way that when set on a table, the subject would sit on one side facing a console, while the experiment

On the subjects's console were three lights:red, yellow and green, from left to right, across the upper portion of the console. At the bottom of this same console was a brass "starting point" button, on which the subject had to keep his finger until required to respond to onset of a stimulus. In an arc above this button were three response keys, also in the order of red, yellow and green, from left to right.

The console facing the experimenter consisted of a digital display in the uppermost portion, which registered latency of response from onset

of stimulus in milliseconds. Below this was a reset button which had to be pressed before the onset of the next stimulus. This set the registered time back to nought milliseconds.

At the right side of the machine on the experimenters side, was an inverting switch, used to interchange the connections between the red and green response keys and the red and green lights, as required in the "reversed" timing condition.

To summarize: the reaction timer is a three-choice visual reaction timer, utilizing touch sensitive response keys and a digital display registering milliseconds for latency of response from onset of stimulus. The machine had a capacity for inverting two of the response systems to their respective stimuli.

APPENDIX 2

REACTION TIME LIGHTING SEQUENCE.

Practice Sequence:

1. Red
2. Yellow
3. Red
4. Red
5. Green
6. Green
7. Yellow
8. Green
9. Green
10. Yellow

Test Sequence:

1. Green
2. Green
3. Yellow
4. Red
5. Red
6. Green
7. Yellow
8. Red
9. Yellow
10. Red
11. Green
12. Green
13. Red
14. Red
15. Yellow
16. Yellow
17. Red
18. Yellow
19. Green
20. Yellow
21. Green
22. Red
23. Green
24. Yellow
25. Green
26. Red
27. Red
28. Green
29. Yellow
30. Yellow

APPENDIX 3

INSTRUCTIONS GIVEN TO SUBJECTS FOR REACTION TIME TESTING

A. Standard Condition:

The test you are about to do measures your reaction time. On the console in front of your are three lights: red, yellow and green, from left to right, and below these, in an arc, are three correspondingly coloured push buttons which turn these lights off. Thus, for example, the yellow light is terminated by the yellow push button and cannot be terminated by either the red or the green push buttons.

Below the push buttons is a brass button. The index finger of your dominant hand (that is, your writing hand) must be placed on this before any light might come on.

When a light comes on, move your index finger to the relevant push button and press this as fast as possible. This will turn the light off. Then immediately put your index finger back on the brass button in preparation for the next light coming on, and repeat the procedure.

The first few times the lights come on will be for practice, to allow you to get used to the procedure.

Remember the object of this test is to press the right button as fast as possible, but your finger must be on the brass button when the light come on.

Concentrate on the lights: please do not talk during the test. Do you understand the procedure? If not, you may ask questions now.

Are you ready? I am starting the machine now.

B. Reversed Condition:

Now the task is slightly different. The procedure is the same as last time, except that now you must press the green push button to extinguish the red light, and you must press the red push button to extinguish the green light. You must still press the yellow push button to extinguish the yellow light. It is only the red and green push buttons which have been reversed. Otherwise the procedure is exactly the same.

Do you understand the instructions? Would you like the instructions repeated? Have you any questions about the procedure? If so, you may ask questions now.

Are you ready? I am starting the machine now.

APPENDIX 4

PROCEDURE OF ADMINISTRATION AND INSTRUCTIONS GIVEN TO SUBJECTS RELATING TO THE MODIFIED CARD SORTING TEST

(For a full description of the cards used, see Nelson, 1976)

Four key cards are placed in line before the subject, in increasing order of items appearing on each, from his left to right. He is given a shuffled pack of forty eight cards to match against the key cards.

The subject is instructed: "Here we have four key cards." (The examiner indicates the cards on the table). "I want you to sort these cards" (indicating those held by the subject) "under the key cards according to certain rules, but the whole point of the test is that I shall not tell you what the rule is. I want you to find that out by trying out different rules, and each time I shall tell you whether it's right or wrong. Now go ahead and try to find out the rule".

The subject commences piling cards beneath the key cards using a set of either colour, shape or number. That used in placing the first card is deemed correct, and the subject is informed after each placement whether he is correct or not under the operative set.

When six consecutive placements have been deemed correct, the set is changed. The subject is instructed: "The rules have now changed. I want you to find a different rule". The subject must now adopt a different sorting set to that hitherto used, the procedure being otherwise the same.

When six consecutive placements of the second set have been deemed correct, the set is changed again, the subject being instructed: "The rules have now changed again. I want you to find another rule you have not used before". This precise wording is used to prevent the subject from returning to his first sorting set.

At the completion of the third set, the subject is instructed to repeat the cycle. He is instructed: "The rules have now changed. I want you to use the rule you first used". At the ends of the fourth and fifth sets, the words "first used" are replaced by "used the second time" and "used the third time" respectively.

Sorting ceases either when six sets have been completed, or when all forty eight cards have been sorted. At no time are the sets named by the examiner.

Scoring

Sorting is scored in terms of number of cards required to complete the task, number of sets completed, total number of errors and total number of perseverative errors, using for the latter, Nelson's (1976) criterion.

APPENDIX 5

INSTRUCTIONS GIVEN TO SUBJECTS FOR LIST LEARNING TASKS

A. Under Selective Reminding Conditions:

I am going to read you a list of twenty words. When I have finished I want you to verbally recall as many of the words as you can, in any order. After you have done this, I will remind you only of those you have omitted to recall, and then I want you to recall as many of these words, and those that you recalled the first time, as you can.

When you have done this, I will remind you of all those words you have omitted to recall, and then I want you to again attempt to recall as many of these words as you can as well as those you recalled the previous time.

Before I start reading the list I will say: "Are you ready? Here are the words".

When I finish the list, I will say: "Now recall as many of the words as you can".

There is no time limit. Do you have any questions.

B. Under Restricted Reminding Conditions:

We are now going to do a test very similar to the one we have just done, but there will be one difference.

I will only remind you of words you have not yet recalled on any trial. If you recall a word on the first trial, you will not be reminded of it even if you fail to recall it the second time.

Do you understand the instructions? Do you have any questions?

APPENDIX 6

LISTS OF WORDS USED IN LIST LEARNING TASKS, AND THEIR ASSOCIATED THORNDIKE-LORGE RATINGS.

SELECTIVE REMINDING						RESTRICTED REMINDING					
ASSESSMENT						ASSESSMENT					
1		2		3		1		2		3	
Chair	AA	Shoulder	AA	Swallow	48	Window	AA	Collar	44	Field	AA
Table	AA	Foot	AA	Fly	AA	Door	AA	Blouse	9	Gorge	9
Sofa	14	Tooth	47	Pig	44	Roof	AA	Ring	AA	Glen	10
Desk	A	Lung	15	Grasshopper	14	Wall	AA	Jersey	21	Hill	AA
Lamp	A	Arm	AA	Centipede	--	Floor	AA	Shirt	47	Equator	8
Dresser	7	Kidney	5	Jackal	2	Ceiling	23	Garter	5	Stream	AA
Television	1	Mouth	AA	Dog	AA	Room	AA	Tie	AA	Bay	AA
Stool	16	Trunk	48	Locust	7	Basement	8	Overcoat	12	Jungle	16
Carpet	24	Knee	AA	Goat	A	Brick	49	Skirt	A	Valley	AA
Bookcase	3	Heart	AA	Lamb	45	Hall	AA	Blazer	--	Desert	A
Kist	--	Shin	5	Horse	AA	Staircase	9	Sock	12	River	AA
Piano	26	Knuckle	5	Rabbit	43	Chimney	30	Shoe	AA	Tropic	9
Radio	41	Toe	35	Spider	24	Foundation	A	Scarf	14	Bank	AA
Picture	AA	Ear	AA	Okapi	--	Attic	12	Glove	43	Meadow	47
Bed	AA	Neck	AA	Bear	AA	Cement	17	Cap	A	Island	AA
Mirror	46	Ankle	21	Hawk	22	Wood	AA	Shorts	2	Mountain	AA
Refrigerator	11	Tongue	A	Bee	A	Bathroom	9	Cardigan	--	Continent	45
Chest *	41	Liver	10	Donkey	16	Glass	AA	Trousers	21	Ditch	28
Hi-fi	--	Hair	AA	Beetle	11	Beam	42	Belt	48	Plain	AA
Stove	40	Leg	AA	Giraffe	1	Kitchen	AA	Hat	AA	Gulf	33

* Chest of Drawers

\- Denotes unlisted word

AA : > 100

A : > 50

Moderate : 11-49

Low : 1-10

Frequency Characteristics of Lists

ASSESSMENT	Selective Condition 1	2	3	Restricted Condition 1	2	3
AA Frequency	4	10	4	10	4	10
A Frequency	2	1	2	1	2	1
Moderate Frequency	9	5	9	6	9	4
Low Frequency	3	4	3	3	3	5
Unlisted Frequency	2		2		2	

Testing for qualitive differences in the lists frequences by means of X^2, the following values are found for the lists used at Assessment 2:

AA and A combined : $X^2 = 1,47$, df = 1, not significant

Moderates : $X^2 = 1,14$, df = 1, not significant

Low and unlisted combined : $X^2 = 0,11$, df = 1, not significant

AA alone : $X^2 = 2,57$, df = 1, not significant

It can therefore be concluded that the lists do not differ significantly in difficulty.

Jointly in a 3 x 2 X^2, the difference between the lists is $X^2 = 12,96$ (df = 2) which is not significant.

APPENDIX 7

SERIAL 3 s : INSTRUCTIONS TO SUBJECTS

The subject is told: "When I say "Begin", I want you to start at 100 - you must say "one hundred" - and count backwards in threes as rapidly as you can. Are you ready? Begin".

After 30 seconds the Subject is told: "Stop".

Serial 3 s : Scoring

Scoring in terms of (a) the number of items covered in 30 seconds, irrespective of whether these are right or wrong, (b) the number of errors made (accuracy) and (c) the number of items correct in 30 seconds.

Notes:

1. At assessments 2 and 3, the numbers commenced at are 99 and 98 respectively.

2. An item is deemed correct if the subtraction from the previous number uttered, be that correct or not, is correct.

APPENDIX 8

INGLIS PAIRED ASSOCIATE LEARNING TEST: THREE ALTERNATE FORMS

FORM A		FORM B		FORM C	
Stimulus	Response	Stimulus	Response	Stimulus	Response
Cabbage	Pen	Flower	Spark	Tree	Fork
Knife	Chimney	Table	River	Cloud	Drum
Sponge	Trumpet	Bottle	Comb	Kettle	Book

Form C is an unstandardized form, based on equivalent word frequencies to Forms A and B. (H. Oblowitz, 1982).

APPENDIX 9

PROCEDURE OF ADMINISTRATION AND INSTRUCTIONS GIVEN TO SUBJECTS RELATING TO THE INGLIS PAIRED-ASSOCIATE LEARNING TEST

The subject is told: "I am going to read you a list of words, two at a time. Listen carefully, because after I finish I shall expect you to remember the words that go together. For example, if the words were "East - West", "Gold - Silver", then when I said the word "East", I should expect you to answer "West", and when I said the word "Gold", you would of course answer .....?" The examiner pauses here to allow the subject to supply the word "Silver". Should the subject not be able to supply the word, the examiner tells him.

The examiner then continues: "Do you understand?" Should the subject indicate lack of understanding, the instructions are repeated to this point, and when confirmation is given the examiner proceeds: "Now listen carefully to the list as I read it".

The examiner then presents the appropriate form of the test for the particular testing session. Word pairs are presented without temporal lapses between the two elements, and five seconds elapses between the end of presentation of one pair and the commencement of the next. Three pairs are presented and five seconds after the last pair, the first stimulus word is presented in the form: "What went with .....?".

Subjects are given ten seconds to respond. In the cases of a correct response within the time limit, the subject is told: "That's right" before presentation of the next stimulus word. Should the subject exceed the time limit or give the wrong associate, he is told the correct associate before presentation of the next stimulus word.

Paired associates are presented to a criterion of three consecutive correct responses. Pairs are presented in random order and once the first pair is eliminated, the remaining two pairs are alternated. When two pairs have been learned, and only one remains, the stimulus word of the remaining pair is presented in alternation with one of

the stimulus words from an already-learned pair, but only the former is scored. The maximum presentations of any stimulus word is thirty.

Scoring

Scoring is in terms of the number of times the response word has to be supplied to the subject, including the original presentations of full-paired associates, yielding a minimum (best) score of three and a maximum (worst) score of ninety three.

APPENDIX 10

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION

For each item select the 'cue' which best characterizes the patient

Item	Scores	Cue
1. Depressed mood (Sadness, hopeless, helpless, worthless)	[0]	Absent
	[1]	These felling states indicated only on questioning
	[2]	These feeling states spontaneously reported verbally
	[3]	Communicates feeling states non-verbally–i.e., throught facial expression, posture, voice, and tendency to weep
	[4]	Patient reports virtually only these feeling states in his spontaneous verbal and non-verbal communication
2. Feelings of guilt	[0]	Absent
	[1]	Self-reproach, feels he has let people down
	[2]	Ideas of guilt or rumination over past errors or sinful deeds
	[3]	Present illness is a punishment. Delusions of guilt
	[4]	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. Suicide	[0]	Absent
	[1]	Feels life is not worth living
	[2]	Wishes he were dead or any thoughts of possible death to self
	[3]	Suicide ideas or gesture
	[4]	Attempts at suicide (any serious attempt rates 4)
4. Insomnia – early	[0]	No difficulty falling asleep
	[1]	Complains of occasional difficulty falling asleep–i.e., more than 1/2 hour
	[2]	Complains of nightly difficulty falling asleep
5. Insomnia – middle	[0]	No difficulty
	[1]	Patient complains of being restless and disturbed during the night
	[2]	Waking during the night–any getting out of bed rates 2 (except for purposes of voiding)
6. Insomnia – late	[0]	No difficulty
	[1]	Waking in early hours of the morning but goes back to sleep
	[2]	Unable to fall asleep again if gets out of bed
7. Work and activities	[0]	No difficulty
	[1]	Thoughts and feelings of incapacity, fatigue or weakness related to activities: work or hobbies
	[2]	Loss of interest in activity; hobbies or work–either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
	[3]	Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
	[4]	Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted

APPENDIX 10

(Cont...)

Item	Scores	Cue
8. Retardation (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)	[0]	Normal speech and thought
	[1]	Slight retardation at interview
	[2]	Obvious retardation at interview
	[3]	Interview difficult
	[4]	Complete stupor
9. Agitation	[0]	None
	[1]	'Playing with' hands, hair, etc.
	[2]	Hand-wringing, nail-biting, hair-pulling, biting of lips
10. Anxiety psychic	[0]	No difficulty
	[1]	Subjective tension and irritability
	[2]	Worrying about minor matters
	[3]	Apprehensive attitude apparent in face or speech
	[4]	Fears expressed without questioning
11. Anxiety somatic	[0]	Absent — **Physiological concomitants of anxiety, such as:**
	[1]	Mild — Gastro-intestinal—dry mouth, wind, indigestion, diarrhea, cramps, belching
	[2]	Moderate — Cardio-vascular—palpitations, headaches
	[3]	Severe — Respiratory—hyperventilation, sighing Urinary frequency
	[4]	Incapacitating — Sweating
12. Somatic symptoms gastro-intestinal	[0]	None
	[1]	Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
	[2]	Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for G. I. symptoms.
13. Somatic symptoms general	[0]	None
	[1]	Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatiguability
	[2]	Any clear-cut symptom rates 2
14. Genital symptoms	[0]	Absent — Symptoms such as: Loss of libido
	[1]	Mild — Menstrual disturbances
	[2]	Severe — [9] Not ascertained
15. Hypochondriasis	[0]	Not present
	[1]	Self-absorption (bodily)
	[2]	Preoccupation with health
	[3]	Frequent complaints, requests for help, etc.
	[4]	Hypochondrical delusions

APPENDIX 10

(Cont...)

Item	Scores	Cue
16. Loss of weight		**A. When rating by history:**
	[0]	No weight loss
	[1]	Probable weight loss associated with present illness
	[2]	Definite (according to patient) weight loss
		B. On weekly ratings by ward psychiatrist, when actual weight changes are measured:
	[0]	Less than 1 lb. (500 g) weight loss in week
	[1]	Greater than 1 lb. (500 g) weight loss in week
	[2]	Greater than 1 lb. (1 kg) weight loss in week
17. Insight	[0]	Acknowledges being depressed and ill
	[1]	Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
	[2]	Denies being ill at all

APPENDIX 11

G.S.H.-M/15/4/1 PARTICIPATION SOLICITING LETTER TP.10/79/4000

WILLIAM SLATER HOSPITAL/HOSPITAAL

(DIVISION OF AFDELING VAN GROOTE SCHUUR HOSPITAL/HOSPITAAL)

TEL.: 65-5116

REPLY TO: SKRYF AAN: MED. SUPERINTENDENT

PLEASE QUOTE / MELD ASB.
Section
Seksie
Ref. / Verw.

Private Bag / Privaatsak x9,
Rondebosch, 7700
C/o-H/V Milner & Park Roads / Weg,
Rondebosch, Cape / Kaap.

This hospital is co-operating with the Department of Pharmacology, Groote Schuur Hospital, in a research project.

A new medication has recently been developed which is claimed to have a very positive effect on memory and other brain functions.

As you are probably aware, alcohol used in excess over a period of time can have adverse effects upon brain functioning. We would like to test this medication which is called Piracetam and we would appreciate your co-operation. In participating in the trial you could only benefit from the drug which is completely safe and without side-effects. You would take the medication for a limited period of time and then its benefit would be re-assessed.

Would you kindly drop in to see Dr. Fraser at this hospital on at to discuss this matter. If you are unable to keep this appointment or if you have any questions, please telephone 655116.

Looking forward to seeing you,

Yours sincerely,

p.p. IAIN S. FRASER, M.B.,Ch.B.,F.F.Psych.(S.A.)
Consultant-in-Charge.

APPENDIX 12

INFORMED CONSENT FORM

I, ... have been adequately informed of the purpose and risks of the clinical trial to be performed by Drs. I.S. Fraser and A.H. Robins and A.E. Price.

I understand that my participation in this trial is entirely voluntary and that no pressure will be applied to enlist my co-operation. Refusal to participate will in no way affect the quality of my medical treatment and care.

I am free to withdraw from the trial at any stage.

With regard to the above, I hereby agree to act as a subject in this trial which evaluates the use of Piracetam in chronic alcoholism.

Signed ..... Date .....

Witnesses 1. .....

2. .....

APPENDIX 13

CLINICAL AND DEMOGRAPHIC DATA ITEMS RELATING TO SUBJECTS

Inquiries were made of the Subjects as to:

- Name
- Current Address
- Age
- Telephone Numbers
- Employer
- Home Language
- Level of Income
- Current Medical Complaints
- Current Medications
- Subjective Problems Taking Medication
- Length of Drinking History
- Date of Last Drink
- Smoking Behaviour
- Addiction to Any Non-Medical Drugs
- Employer's Awareness of Subjects Alcoholism
- Difficulties at Work regarding Making Appointments at William Slater
- Handedness
- Level of Education

APPENDIX 15

DROP-OUTS AND EXCLUSIONS

Criteria of exclusion applicable to subjects completing the trial were formulated as below:

a. deviation of ten days or more from the pre-determined inter-assessment interval of 56 days.

b. tablet returns for any inter-assessment period exceeding 134, i.e. over 40% of expected consumption.

c. last trial medication taken more than two days prior to assessment, (i.e. after elimination of trial substance from the body (half-life of Piracetam is 7 hours).

Subject attrition per group was as below:

CAUSES	GROUP 1	GROUP 2
Dropping out	4	2
Excessive deviation from inter-assessment interval	1	2
Excessive tablet returns	2	4
Absence of medication for more than two days prior to assessment	0	0
TOTAL:	7	8

Exclusion criteria were applied in descending order (a to c). The failure of criterion c to excise any subjects was due to the prior exclusion of several subjects on criteria a and b.

APPENDIX 16

SUBJECT DESCRIPTIVE DATA

Subject No.	Handedness	Sex	Age	Treatment Group Allocation
1	R	M	57	2
2	L	M	45	1
3	R	M	53	1
4	R	M	50	2
5	R	M	44	1
6	R	M	42	2
7	R	M	38	1
8	R	M	55	2
9	R	M	54	2
10	R	M	41	1
11	R	F	42	1
12	L	M	54	1
13	R	M	43	2
14	R	M	52	2
15	R	M	45	2
16	R	M	58	2
17	R	M	58	2
18	R	M	54	1
19	L	M	48	1
20	R	M	49	1
21	R	M	38	2
22	R	M	51	1
23	R	M	39	1
24	R	M	35	1
25	R	M	58	2
26	R	M	51	2
27	R	M	46	2
28	R	M	49	1
29	R	M	49	1
30	R	M	56	2

Subject No.	Handedness	Sex	Age	Treatment Group Allocation
31	R	M	55	2
32	R	M	36	1
33	R	M	43	1
34	R	F	56	1
35	R	M	53	2
36	R	M	48	1
37	R	M	46	2
38	R	M	42	2
39	R	M	53	2
40	R	F	44	1
41	R	M	48	2
42	R	M	61	2
43	L	M	54	1
44	R	F	39	1
45	R	M	45	2
46	R	F	54	1
47	R	F	56	1
48	R	M	45	2
49	R	M	46	1
50	R	M	35	2
51	R	M	57	1
52	R	M	34,5	2
53	R	M	49	2
54	R	M	36	1
55	R	M	50	1
56	R	M	41	1
57	R	M	40	2
58	R	M	45	2
59	R	M	45	1
60	R	M	47	2

Subject No.	Handedness	Sex	Age	Treatment Group Allocation
61	R	F	55	1
62	R	M	59	1
63	R	F	54	1

KEY:

L = Left handed
R = Right handed
M = Male
F = Female
1 = Placebo - Piracetam order
2 = Piracetam - Placebo order

APPENDIX 17

APPROXIMATE LENGTH OF DRINKING HISTORY, SERIOUS MEDICAL CONDITIONS AND CURRENT MEDICATION OF FULL SAMPLE

Subject	A.D.H.	S.M.H.	MEDICATION
1	37	Coronary thrombosis	E.,J.,R.
2	24	T.L.E.; Pancreatitis	N,A, Evadyne
3	28	Ulcer	C,Q,P.
4	25		B.
5	15		A.L.O.
6	22		C,H,L.
7	15	Asthma	K,L,C, Ventolin
8	35		
9	20	Cancer of throat	L,Q.
10	28	Peptic ulcer; Aneurism (1976)	E,K,C.
11	15		O
12	25	L.B.P.	B,R.
13	23	Peptic ulcer	H,R,A.
14	16		L.
15	15	Peptic ulcer	A,R.
16	41	Emphysema	
17	20		
18	33	Diabetes; cancer of tongue	Q,R.
19	27		A,L,M.
20	15		
21	24		L,Q.
22	18		E,F,Q.
23	18		
24	10		
25	30	T.B.	Q.
26	15		R.

Subject	A.D.H.	S.M.H.	MEDICATION
27	15		A,B,L,O,Lexotan Syndol
28	30	H.B.P.	Moducren
29	12	H.B.P.	H,L,Q, Moducren
30	20		H,A.
31	25		A
32	15	T.L.E.	B,C,D,
33	15	H.B.P.	
34	22	H.B.P.	G,O,R. Hygroton, Imipramine
35	25	Spastic colon	Q,R.
36	13		A,R.
37	20		R,C.
38	15		B,M.
39	30	Pancreatitis, T.B.	H.
40	12		A,K.
41	20		B,C,K.
42	35		Q, Lithium
43	25		L,Q.
44	15		H,K,L,C.
45	18		L,Q,C.
46	11		A,Q, Normison, Tryptanol
47	12	Emphysema	A,L,Q,H, Peterphylin, Mogodon
48	20		B
49	20	Coronary thrombosis; H.B.P.	B,C, Zyloprim
50	10	Peptic ulcer; Hiatus hernia	B,C,Merasyn Fabahistin
51	35		Q,R.
52	15		
53	16		A,B,E,L,Q
54	11		C,E,R.
55	25	H.B.P.	Q,R,A, Navidrex Lopressor
56	20		A,Q,R.
57	15		B,C.

Subject	A.D.H.	S.M.H.	MEDICATION
58	-		
59	-		
60	25	Chronic diarrhoea	K, Eglonyl
61	25	H.B.P.	E,A,B,M, Triazolam, Pertofrin, Halcion, Desipramine
62	15	Asthma	L, Meticortin
63	20		

Abbreviations:

T.L.E. = Temporal lobe epilepsy
H.B.P. = High blood pressure
L.B.P. = Low blood pressure
A.D.H. = Approximate drinking history
S.M.H. = Serious medical history
T.B. = Tuberculosis

Medication Key:

A	Disulfiram	K	Dothiepin
B	Lorazepam	L	Oxazepam
C	Calcium carbimide	M	Trimipramine
D	Phenytoin	N	Carbamazepine
E	Propranolol	O	Imipramine
F	Chlorpromazine	P	Clorazepate
G	Thioridazine	Q	Amitriptyline
H	Nitrazepam	R	Diazepam
J	Perhexiline		

Subjects free of Medication:- Subjects 8,16,17,20,23,24,52,63

Note: Many of the drugs reported above are not issued by William Slater Hospital. Their use has been reported by subjects, and these reports may be both incomplete and inaccurate.

APPENDIX 18

THE INFLUENCE OF PSYCHOTROPIC DRUGS ON RESULTS OBTAINED: STATISTICAL EVALUATIONS OF DIFFERENCES BETWEEN GROUPS

In total, 42 of the final 48 subjects were taking psychotropic drugs as regular medication. Exactly 21 of each group of subjects (Groups 1 and 2) were receiving these.

Chi-squared analysis (Two-by-two test of association) yielded a value of 1,198, for df = 1, which is not significant at ,05 (critical chi-square = 3,841).

It can therefore be concluded that there was no significant difference in proportions of subjects receiving psychotropic drugs in each group.

APPENDIX 19

ISSUES RELATED TO SAMPLE SIZE

Bearing in mind the exploratory nature of this research, it was decided that a significance level of ,01 could not be used, and that bearing in consideration the numerous analyses involved, neither could the ,10 level, frequently used in exploratory research, be used. Consequently, the ,05 level of significance was chosen.

It was also desirable that Type II errors be avoided, and that this indicated the power of the test should be set at 0,95. The most important comparisons possible involve interaction. Consequently, (Gilbert, 1977a) a value of k = 3 was used to obtain a value of $\phi = 2,3$. A relatively small z-value, denoting great accuracy in detecting small differences, was chosen; z = 0,75.

All this allowed for a sample size of approximately 56, derived from the formula:

$$N = \frac{z\ (k^2)\ (\phi^2)}{z^2}$$

The choice of such a balance of factors was considered reasonable in terms of cost-benefit ratio.

However, it was not possible to obtain the required initial number of subjects to arrive at a final figure of 56 after normal subject attrition, and the final sample size was, for most analyses, 48. Using the same values of , 1-B, and k, this need only reduce the value of z used to approximately 0,85, using the above formula.

Thus, values used in this study are: $\alpha = 0,05$

$1-B = 0,95$

$z = \pm 0,85$

APPENDIX 20

RAW DATA

Hamilton Rating Scale for Depression

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	15	1	6	1	1	3	4
3	28	12	14	4	11	4	6
5	4	2	5	6	7	6	8
10	18	13	16	8	3	6	7
11	1	0	1	9	9	4	7
12	6	2	7	13	13	9	15
18	10	5	8	14	5	0	6
20	2	0	5	15	13	14	13
22	2	3	4	21	7	2	7
23	7	3	8	25	9	6	7
24	5	4	8	27	22	19	21
29	10	7	4	30	1	2	0
33	0	3	0	35	6	7	3
34	8	16	10	37	11	8	0
36	2	3	4	41	1	5	9
40	1	1	5	42	0	0	4
43	8	11	6	45	3	5	6
44	18	21	12	48	6	2	4
46	2	2	4	50	9	7	8
47	14	6	4	53	5	7	3
49	9	7	5	57	4	6	13
51	9	2	4	60	14	6	8
54	6	4	4				
56	11	12	4				
61	7	10	9				
63	6	1	5				

Choice Reaction Time (Overall, Standard Condition)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	712	636	612	1	803	751	487
3	720	812	791	4	686	731	690
5	570	659	917	6	560	651	682
10	792	749	716	8	655	840	807
11	507	682	616	9	801	690	565
12	620	736	665	13	651	745	801
18	662	857	951	14	639	688	834
20	555	507	600	15	619	776	800
22	674	673	669	21	505	476	688
23	642	752	724	25	619	761	627
24	681	496	620	27	635	623	560
29	689	754	644	30	576	616	538
33	699	708	627	35	694	915	696
34	663	698	702	37	639	702	575
36	664	775	600	41	604	731	767
40	925	716	571	42	749	714	599
43	1008	894	680	45	1000	1100	781
44	742	656	550	48	703	645	586
46	601	972	669	50	624	713	608
47	837	964	732	53	756	636	706
49	637	662	543	57	860	578	515
51	745	700	659	60	648	591	557
54	793	540	528				
56	930	575	504				
61	677	734	653				
63	761	708	1203				

Choice Reaction Time (Overall, Reversed Condition)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	787	782	755	1	705	721	738
3	728	831	711	4	876	753	809
5	758	797	732	6	704	686	625
10	951	760	745	8	966	758	690
11	683	643	635	9	754	746	713
12	779	717	771	13	1145	924	979
18	882	868	827	14	694	685	710
20	677	592	577	15	829	673	673
22	887	729	723	21	585	647	638
23	792	671	666	25	762	712	668
24	649	616	572	27	811	675	673
29	770	821	728	30	644	638	643
33	870	767	705	35	990	784	776
34	849	815	742	37	839	796	778
36	1158	889	789	41	791	841	822
40	756	666	649	42	784	738	830
43	1052	803	764	45	994	975	944
44	648	702	648	48	847	818	797
46	558	737	772	50	791	690	752
47	914	1014	941	53	680	733	776
49	672	565	594	57	769	676	620
51	838	894	826	60	629	587	630
54	692	655	612				
56	884	761	734				
61	852	897	762				
63	894	807	852				

Choice Reaction Time (Yellow, Standard Condition)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	715	634	671	1	754	759	478
3	734	721	855	4	761	700	725
5	621	630	1185	6	543	621	630
10	766	946	623	8	741	738	959
11	504	851	738	9	773	751	567
12	593	710	608	13	571	700	928
18	703	874	1422	14	644	760	797
20	500	443	561	15	605	900	1117
22	683	747	800	21	520	506	717
23	604	787	691	25	613	808	568
24	483	602	597	27	738	636	593
29	734	747	662	30	637	687	607
33	658	837	579	35	669	1211	776
34	666	636	631	37	640	695	635
36	688	845	541	41	592	721	789
40	817	893	620	42	829	613	599
43	1007	896	700	45	1133	1671	850
44	673	603	557	48	690	678	571
46	698	2001	569	50	713	759	641
47	810	955	758	53	821	657	718
49	635	594	557	57	907	581	468
51	778	584	655	60	493	644	553
54	1000	537	514				
56	930	560	479				
61	693	779	708				
63	792	748	1666				

Choice Reaction Time (Yellow, Reversed Condition)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	742	808	683	1	687	689	679
3	769	785	737	4	816	633	677
5	641	720	637	6	741	708	548
10	881	658	636	8	870	829	707
11	661	640	566	9	685	617	673
12	772	706	682	13	869	846	875
18	965	851	736	14	664	669	641
20	651	592	548	15	801	612	614
22	744	751	604	21	543	703	619
23	786	616	599	25	717	733	629
24	646	556	536	27	890	679	643
29	682	825	621	30	567	632	544
33	714	701	601	35	821	789	742
34	733	699	676	37	729	723	664
36	926	744	718	41	744	768	728
40	637	587	585	42	692	677	814
43	942	710	700	45	879	956	886
44	673	600	562	48	785	744	747
46	634	671	626	50	742	624	707
47	832	776	807	53	679	691	768
49	691	567	550	57	666	609	532
51	818	728	704	60	650	596	590
54	790	714	613				
56	725	555	638				
61	782	876	779				
63	831	795	866				

Choice Reaction Time (Red and Green, Standard)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	711	637	583	1	824	747	490
3	744	852	763	4	649	752	673
5	540	670	802	6	569	666	705
10	801	665	756	8	612	883	731
11	509	598	554	9	817	668	564
12	629	749	690	13	696	768	746
18	642	849	749	14	637	651	853
20	579	534	616	15	625	714	664
22	669	642	604	21	498	462	676
23	661	739	740	25	622	740	652
24	795	450	630	27	591	618	546
29	669	758	637	30	549	569	504
33	719	655	652	35	705	788	661
34	661	729	738	37	638	705	554
36	653	745	629	41	608	736	756
40	979	627	553	42	715	765	599
43	1009	894	662	45	942	856	747
44	772	666	544	48	708	629	594
46	560	659	736	50	580	671	592
47	852	971	719	53	718	616	694
49	637	729	536	57	840	531	539
51	731	805	661	60	715	547	562
54	689	542	542				
56	930	586	516				
61	663	711	598				
63	733	671	741				

Choice Reaction Time (Red and Green, Reversed)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	812	770	786	1	715	737	768
3	709	848	700	4	907	796	866
5	816	824	773	6	723	677	663
10	985	811	785	8	1001	723	681
11	693	644	665	9	788	793	733
12	782	723	809	13	1305	958	1024
18	847	875	866	14	705	691	744
20	688	592	591	15	841	699	698
22	949	719	783	21	610	615	645
23	795	695	700	25	785	703	680
24	651	641	591	27	782	673	686
29	807	820	761	30	685	641	679
33	937	796	757	35	1075	782	793
34	907	873	766	37	886	826	835
36	1257	962	825	41	819	872	885
40	815	700	677	42	829	773	846
43	1108	850	828	45	1043	982	973
44	638	733	691	48	877	852	823
46	525	761	845	50	812	755	774
47	954	1134	1008	53	681	775	780
49	663	565	616	57	820	709	664
51	846	976	887	60	622	582	651
54	643	625	612				
56	953	864	783				
61	899	907	754				
63	925	813	845				

Purdue Pegboard Test - Preferred Hand Task

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	38	46	41	1	42	39	43
3	44	43	45	4	47	46	48
5	42	36	41	6	47	51	49
10	47	48	49	8	48	49	51
11	51	47	48	9	38	44	41
12	47	45	41	13	33	34	37
18	43	42	42	14	49	47	50
20	48	46	48	15	44	39	40
22	52	54	51	21	48	50	48
23	45	53	48	25	48	48	53
24	55	50	49	27	37	41	45
29	36	38	43	30	36	40	41
33	41	41	38	35	33	33	36
34	40	42	41	37	39	42	48
36	38	44	44	41	48	49	52
40	39	45	42	42	32	35	34
43	38	41	39	45	38	42	47
44	52	48	49	48	49	49	52
46	40	39	41	50	46	52	46
47	30	33	34	53	39	39	39
49	33	38	39	57	44	44	36
51	44	39	42	60	44	48	47
54	39	43	47				
56	37	42	44				
61	36	35	38				
63	45	47	49				

Purdue Pegboard Test - Non-Preferred Hand Task

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	31	35	37	1	37	38	40
3	46	42	45	4	42	48	44
5	42	36	42	6	47	46	45
10	39	46	36	8	46	45	43
11	51	45	50	9	42	46	43
12	42	44	40	13	34	36	37
18	36	39	37	14	47	47	49
20	45	46	43	15	39	38	41
22	47	51	49	21	46	45	47
23	48	47	47	25	47	48	51
24	54	51	50	27	39	40	40
29	38	38	38	30	42	39	43
33	32	38	36	35	36	39	39
34	41	41	43	37	47	41	47
36	36	43	46	41	44	47	46
40	40	43	42	42	37	34	35
43	33	41	38	45	38	40	40
44	54	47	51	48	40	47	45
46	33	35	37	50	44	45	46
47	33	32	35	53	40	36	41
49	37	39	40	57	38	42	33
51	34	36	42	60	43	43	43
54	39	39	45				
56	32	38	39				
61	40	37	41				
63	41	40	44				

Purdue Pegboard Test - Simultaneous Hands Task

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	25	31	28	1	34	34	37
3	32	35	31	4	36	34	33
5	34	33	30	6	35	42	38
10	37	33	39	8	37	35	37
11	44	41	38	9	32	35	34
12	37	35	33	13	24	23	24
18	34	35	35	14	42	40	38
20	35	31	36	15	32	29	31
22	42	45	44	21	37	39	38
23	38	36	39	25	39	38	40
24	43	41	41	27	31	31	35
29	35	31	31	30	31	31	31
33	28	30	30	35	27	24	29
34	32	29	33	37	35	35	38
36	29	33	35	41	42	41	40
40	33	37	34	42	30	29	29
43	30	28	27	45	30	33	33
44				48	32	38	34
46	28	25	28	50	38	40	36
47	24	27	25	53	29	33	33
49	26	30	26	57	32	36	31
51	30	28	29	60	34	35	36
54	32	34	37				
56	31	28	31				
61	28	21	28				
63	39	37	40				

WAIS Information Subtest

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	17	16	17	1	17	14	17
3	15	16	17	4	22	22	22
5	24	23	22	6	12	16	15
10	13	15	16	8	19	19	18
11	22	22	20	9	13	11	13
12	19	17	18	13	13	14	13
18	14	14	16	14	19	18	20
20	20	19	20	15	10	11	11
22	21	19	18	21	15	15	16
23	18	22	21	25	18	16	15
24	16	16	16	27	17	18	21
29	21	18	19	30	16	16	20
33	17	19	17	35	16	20	20
34	11	14	15	37	10	11	11
36	15	16	16	41	18	18	16
40	19	21	23	42	18	19	21
43	12	11	11	45	11	9	10
44	14	15	17	48	18	18	17
46	19	20	21	50	21	23	21
47	15	15	16	53	15	13	13
49	24	25	24	57	7	10	10
51	12	12	13	60	17	18	17
54	14	16	17				
56	16	18	17				
61	13	13	15				
63	13	15	16				

WAIS Digit Span Subtest

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	12	13	11	1	14	14	14
3	11	10	11	4	11	10	10
5	11	11	12	6	10	12	15
10	10	14	13	8	12	12	12
11	15	16	16	9	10	10	12
12	14	13	14	13	11	11	11
18	9	7	8	14	9	10	8
20	12	17	16	15	11	11	12
22	10	13	13	21	12	15	15
23	10	12	11	25	11	11	11
24	13	13	13	27	9	11	11
29	12	12	13	30	11	14	14
33	7	9	9	35	10	9	10
34	10	10	11	37	8	9	7
36	9	9	9	41	13	9	13
40	10	10	13	42	8	9	10
43	8	9	9	45	12	13	13
44	13	12	12	48	9	11	11
46	11	11	12	50	16	15	16
47	11	10	11	53	12	10	8
49	16	15	13	57	12	14	11
51	9	9	8	60	11	14	12
54	11	12	13				
56	9	9	9				
61	8	8	7				
63	12	12	10				

WAIS Digits Forwards

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	7	7	5	1	8	7	8
3	6	5	6	4	6	6	5
5	6	6	7	6	5	7	9
10	7	8	7	8	7	8	7
11	7	8	8	9	4	5	6
12	7	6	7	13	8	7	7
18	5	4	5	14	5	6	4
20	7	9	9	15	6	7	7
22	5	8	8	21	7	8	8
23	6	7	7	25	6	5	5
24	9	8	8	27	5	6	6
29	5	5	6	30	7	8	7
33	4	6	6	35	6	4	5
34	6	6	6	37	4	5	4
36	6	6	6	41	8	5	8
40	5	5	7	42	5	6	7
43	5	7	6	45	6	8	7
44	7	8	8	48	6	7	6
46	6	6	7	50	8	7	8
47	6	5	7	53	7	6	5
49	8	8	6	57	6	8	6
51	6	6	5	60	6	8	6
54	7	5	6				
56	6	6	6				
61	4	5	4				
63	7	7	6				

WAIS Digits Backwards

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	5	6	6	1	6	7	6
3	5	5	5	4	5	4	5
5	5	5	5	6	5	5	6
10	3	6	6	8	5	4	5
11	8	8	8	9	6	5	6
12	7	7	7	13	3	4	4
18	4	3	3	14	4	4	4
20	5	8	7	15	5	4	5
22	5	5	5	21	5	7	7
23	4	5	4	25	5	6	6
24	4	5	5	27	4	5	5
29	7	7	7	30	4	6	7
33	3	3	3	35	4	5	5
34	4	4	5	37	4	4	3
36	3	3	3	41	5	4	5
40	5	5	6	42	3	3	3
43	3	2	3	45	6	5	6
44	6	4	4	48	3	4	5
46	5	5	5	50	8	8	8
47	5	5	4	53	5	4	3
49	8	7	7	57	6	6	5
51	3	3	3	60	5	6	6
54	4	7	7				
56	3	3	3				
61	4	3	3				
63	5	5	4				

WAIS Similarities Subtest

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	14	13	17	1	19	19	19
3	12	14	13	4	20	21	21
5	21	20	21	6	15	18	14
10	10	12	12	8	19	20	19
11	19	19	17	9	13	14	12
12	18	21	19	13	11	14	11
18	13	11	13	14	16	14	14
20	19	22	20	15	7	9	11
22	16	18	18	21	19	20	17
23	17	18	15	25	20	23	20
24	19	22	21	27	18	20	19
29	20	18	20	30	15	18	21
33	15	14	15	35	15	13	14
34	9	12	15	37	13	13	15
36	14	13	15	41	16	10	16
40	19	17	17	42	19	20	19
43	4	8	5	45	9	15	15
44	14	17	15	48	13	17	19
46	18	18	20	50	18	19	18
47	15	14	13	53	15	13	12
49	22	22	19	57	15	13	12
51	17	18	18	60	20	21	23
54	21	19	21				
56	15	18	17				
61	16	17	19				
63	15	16	15				

WAIS Object Assembly Subtest

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	19	19	19	1	11	19	19
3	15	21	21	4	21	21	22
5	13	17	18	6	21	21	20
10	6	12	14	8	10	12	13
11	17	24	25	9	16	16	15
12	17	19	18	13	15	15	12
18	17	19	17	14	16	20	21
20	19	21	24	15	17	19	20
22	13	21	18	21	17	21	23
23	7	9	12	25	20	19	21
24	19	21	23	27	12	12	19
29	19	19	18	30	13	18	22
33	10	14	13	35	17	18	18
34	15	17	19	37	16	17	19
36	13	16	22	41	20	21	22
40	12	14	17	42	22	20	24
43	14	12	15	45	21	23	22
44	18	19	20	48	11	22	22
46	17	20	18	50	14	15	19
47	12	16	17	53	14	19	19
49	18	20	20	57	18	19	18
51	12	22	17	60	17	18	18
54	17	23	24				
56	19	15	18				
61	14	15	18				
63	13	11	19				

WAIS Block Design Subtest

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	20	21	21	1	23	23	24
3	18	20	24	4	32	34	35
5	11	12	13	6	33	31	32
10	15	20	21	8	14	16	16
11	32	29	34	9	19	23	23
12	16	16	19	13	19	19	20
18	13	19	20	14	25	23	25
20	33	32	29	15	21	20	20
22	22	24	24	21	25	32	33
23	25	25	26	25	29	29	29
24	24	29	25	27	18	20	25
29	23	23	23	30	27	23	31
33	16	15	12	35	23	21	25
34	17	16	21	37	17	13	17
36	10	16	13	41	32	34	32
40	22	25	24	42	29	30	32
43	9	16	15	45	32	31	36
44	19	28	19	48	25	21	26
46	28	29	27	50	21	26	28
47	12	10	15	53	19	20	23
49	28	32	31	57	32	31	32
51	23	22	20	60	25	19	23
54	32	37	34				
56	21	24	25				
61	15	19	15				
63	21	22	22				

WAIS Digit Symbol Substitution Test

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	30	34	31	1	37	37	32
3	30	28	31	4	50	50	57
5	32	36	32	6	42	51	55
10	37	44	51	8	33	40	43
11	50	48	48	9	26	29	29
12	24	31	30	13	22	25	24
18	21	22	22	14	26	30	31
20	38	48	45	15	24	23	26
22	30	47	43	21	45	49	49
23	41	46	47	25	37	46	44
24	44	51	51	27	43	43	45
29	44	41	37	30	38	42	52
33	28	31	35	35	25	28	32
34	23	22	25	37	23	23	25
36	22	28	26	41	20	24	26
40	42	44	44	42	27	27	34
43	17	20	22	45	30	30	35
44	37	35	39	48	31	29	38
46	37	44	31	50	33	34	42
47	35	36	40	53	38	41	33
49	53	52	55	57	32	43	41
51	27	31	29	60	47	46	47
54	41	46	53				
56	22	32	29				
61	24	25	30				
63	48	47	51				

WAIS Pro-Rated IQ

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	106	106	108	1	114	119	119
3	98	108	111	4	132	134	140
5	108	113	113	6	112	122	120
10	86	103	105	8	107	113	112
11	127	137	138	9	97	99	101
12	109	114	113	13	90	93	93
18	90	91	93	14	105	109	116
20	122	140	139	15	89	93	93
22	106	124	116	21	110	125	127
23	97	108	108	25	123	128	119
24	113	125	124	27	100	108	119
29	122	114	116	30	109	119	140
33	87	93	92	35	102	103	109
34	93	98	108	37	84	86	88
36	84	91	99	41	111	105	115
40	106	108	117	42	117	118	131
43	74	84	84	45	107	113	117
44	100	108	99	48	93	113	120
46	114	122	120	50	110	115	122
47	100	98	106	53	102	101	96
49	141	145	134	57	103	110	104
51	101	114	102	60	116	120	123
54	113	127	127				
56	97	102	102				
61	93	98	100				
63	106	107	111				

MCST - Total cards presented

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	45	43	39	1	45	43	36
3	48	48	48	4	36	36	37
5	48	40	41	6	36	37	43
10	48	48	48	8	38	48	39
11	38	40	42	9	47	48	48
12	37	37	37	13	48	37	47
18	48	46	48	14	48	42	45
20	36	36	36	15	48	48	46
22	48	38	42	21	44	48	36
23	44	43	42	25	47	36	38
24	38	36	36	27	36	36	45
29	48	43	48	30	42	48	46
33	48	48	43	35	48	48	48
34	48	48	48	37	48	48	48
36	48	48	48	41	37	41	40
40	47	38	39	42	37	37	36
43	48	48	48	45	39	38	37
44	44	48	42	48	43	48	38
46	48	46	41	50	36	43	39
47	48	48	48	53	42	48	37
49	36	36	41	57	48	42	41
51	48	48	42	60	37	42	42
54	48	48	48				
56	48	48	45				
61	48	48	39				
63	48	48	48				

MCST - Sets completed

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	6	6	6	1	6	6	6
3	5	2	3	4	6	6	6
5	4	6	6	6	6	6	6
10	2	2	1	8	6	5	6
11	6	6	6	9	6	5	5
12	6	6	6	13	5	6	6
18	1	2	2	14	5	6	6
20	6	6	6	15	6	5	6
22	4	6	6	21	6	6	6
23	6	6	6	25	6	6	6
24	6	6	6	27	6	6	6
29	5	6	5	30	6	4	6
33	3	5	6	35	2	2	1
34	2	1	1	37	1	4	4
36	1	1	0	41	6	6	6
40	6	6	6	42	6	6	6
43	2	2	2	45	6	6	6
44	6	5	6	48	6	5	6
46	4	6	6	50	6	6	6
47	5	5	5	53	6	5	6
49	6	6	6	57	5	6	6
51	2	5	6	60	6	6	6
54	1	0	2				
56	5	4	6				
61	5	5	6				
63	1	5	4				

MCST - Total Errors

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	7	7	2	1	5	3	0
3	10	27	19	4	0	0	1
5	14	2	1	6	0	1	4
10	28	25	28	8	2	4	2
11	1	1	1	9	10	13	10
12	1	1	1	13	6	1	4
18	28	27	22	14	12	5	5
20	0	0	0	15	7	6	7
22	14	1	1	21	6	7	0
23	5	6	1	25	10	0	2
24	2	0	0	27	0	0	5
29	9	2	6	30	3	12	6
33	18	15	2	35	35	16	23
34	29	27	29	37	42	17	14
36	27	29	34	41	1	4	2
40	6	2	1	42	1	1	0
43	29	23	27	45	3	2	1
44	7	8	2	48	6	6	2
46	14	3	2	50	0	2	1
47	14	10	15	53	5	13	1
49	0	0	1	57	7	3	4
51	30	10	4	60	1	2	1
54	33	39	17				
56	3	18	4				
61	18	13	3				
63	34	10	16				

MCST - Perseverative Errors

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	0	2	1	1	-	-	-
3	2	8	3	4	0	0	0
5	5	0	0	6	0	0	1
10	10	6	4	8	0	0	0
11	0	0	0	9	5	4	5
12	1	1	1	13	2	0	2
18	9	6	5	14	5	0	1
20	0	0	0	15	1	1	2
22	2	0	0	21	3	2	0
23	1	0	0	25	5	0	0
24	0	0	0	27	0	0	1
29	2	0	0	30	1	2	1
33	5	5	0	35	21	5	4
34	7	1	3	37	42	7	1
36	7	9	13	41	0	1	0
40	2	0	0	42	0	0	0
43	7	8	7	45	3	1	0
44	0	0	1	48	1	1	0
46	9	1	0	50	0	0	0
47	5	2	3	53	1	5	0
49	0	0	0	57	1	1	1
51	15	0	0	60	1	0	0
54	9	7	4				
56	0	2	2				
61	3	3	1				
63	8	2	4				

Selective Reminding List Learning (Total Scores)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	39	51	39	1	46	50	51
3	32	44	35	4	53	55	55
5	33	29	28	6	46	44	37
10	37	55	39	8	43	43	34
11	51	48	47	9	43	52	48
12	34	48	33	13	29	26	19
18	22	35	36	14	36	47	36
20	54	51	44	15	38	52	35
22	35	42	42	21	46	50	36
23	52	47	43	25	51	57	45
24	42	52	49	27	44	46	35
29	52	54	39	30	42	50	38
33	43	43	40	35	39	48	39
34	36	40	28	37	47	43	28
36	32	39	30	41	46	49	39
40	46	41	39	42	31	52	28
43	33	36	28	45	28	37	29
44	52	46	34	48	38	39	35
46	54	52	40	50	42	50	37
47	35	52	45	53	29	31	30
49	54	53	51	57	42	35	27
51	40	39	33	60	20	47	30
54	47	53	32				
56	46	38	38				
61	39	41	31				
63	42	46	39				

Selective Reminding List Learning (Amount of List Learned)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	9	18	11	1	13	15	16
3	7	13	8	4	18	19	20
5	5	6	4	6	13	12	9
10	8	18	10	8	12	11	8
11	16	15	14	9	8	19	13
12	5	14	9	13	5	4	1
18	6	10	9	14	9	14	8
20	18	17	13	15	11	17	10
22	8	14	12	21	14	17	10
23	17	15	10	25	18	18	15
24	11	17	14	27	13	13	8
29	16	18	12	30	13	13	11
33	11	12	13	35	8	14	7
34	10	10	6	37	14	11	6
36	4	9	6	41	13	15	9
40	13	10	11	42	8	19	6
43	7	10	8	45	8	10	5
44	17	12	10	48	10	5	8
46	18	18	12	50	10	16	8
47	7	18	17	53	7	7	5
49	19	19	17	57	12	10	6
51	10	9	7	60	4	12	5
54	15	19	8				
56	13	9	13				
61	9	11	7				
63	12	14	11				

Restrictive Reminding List Learning (Total Scores)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	43	52	41	1	51	57	46
3	44	37	35	4	50	58	54
5	33	46	34	6	41	44	44
10	35	49	38	8	36	45	36
11	52	54	45	9	48	55	38
12	34	42	29	13	21	17	15
18	34	39	26	14	39	44	32
20	53	57	50	15	42	44	26
22	40	43	43	21	51	46	37
23	47	47	49	25	60	52	43
24	56	42	46	27	44	47	33
29	46	54	41	30	43	48	43
33	40	39	38	35	35	44	39
34	44	45	32	37	44	48	31
36	27	37	25	41	51	49	44
40	43	43	40	42	35	42	38
43	37	45	31	45	30	35	29
44	44	47	35	48	51	49	34
46	51	55	40	50	47	49	46
47	33	56	30	53	42	33	24
49	54	53	55	57	40	37	29
51	40	41	39	60	31	40	33
54	53	53	48				
56	42	39	25				
61	42	41	37				
63	44	42	36				

Restrictive Reminding List Learning (Amount of List Learned)

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	14	18	12	1	17	20	13
3	13	14	11	4	16	20	16
5	7	15	10	6	10	15	13
10	9	17	9	8	13	15	10
11	20	20	15	9	15	19	10
12	9	14	8	13	4	2	3
18	10	12	7	14	12	15	10
20	19	19	17	15	13	15	6
22	12	14	14	21	17	16	11
23	17	16	17	25	20	16	13
24	19	19	15	27	15	16	8
29	17	19	13	30	14	15	13
33	14	11	13	35	8	15	12
34	13	15	8	37	13	16	9
36	6	10	6	41	17	16	15
40	13	15	12	42	9	13	12
43	10	14	9	45	9	9	6
44	16	16	9	48	18	17	11
46	19	19	13	50	15	18	15
47	9	20	10	53	13	9	5
49	20	19	19	57	15	12	6
51	12	12	11	60	7	11	9
54	18	19	17				
56	14	11	4				
61	15	14	12				
63	13	13	9				

Serial 3s - Correct Enumerations

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	16	14	16	1	25	26	23
3	5	6	6	4	13	16	17
5	20	5	13	6	17	20	21
10	17	21	21	8	13	15	18
11	19	20	21	9	11	9	9
12	9	11	6	13	13	17	19
18	14	12	13	14	8	10	10
20	15	19	22	15	2	8	5
22	30	29	32	21	20	22	13
23	13	16	15	25	19	22	20
24	20	18	19	27	29	27	24
29	11	16	12	30	23	28	22
33	18	21	20	35	16	19	18
34	8	7	13	37	3	7	5
36	4	4	6	41	9	10	9
40	9	20	18	42	14	12	9
43	3	4	5	45	15	16	17
44	12	14	15	48	7	4	4
46	17	16	15	50	22	21	21
47	4	0	12	53	8	7	5
49	33	33	32	57	10	5	2
51	11	14	11	60	20	17	19
54	15	18	21				
56	5	11	14				
61	6	7	8				
63	5	3	2				

Serial 3s - Total Items Enumerated

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	16	15	16	1	25	26	23
3	7	6	6	4	13	17	17
5	21	7	13	6	17	21	21
10	17	23	21	8	14	18	18
11	19	23	23	9	12	10	9
12	9	12	6	13	13	18	19
18	15	13	13	14	10	10	10
20	15	19	22	15	4	9	6
22	30	29	32	21	20	24	13
23	13	17	16	25	19	22	20
24	21	20	19	27	29	27	25
29	11	16	12	30	23	28	22
33	18	21	20	35	16	21	18
34	8	8	13	37	7	8	6
36	4	5	6	41	10	10	9
40	10	20	18	42	14	12	12
43	6	5	9	45	15	16	18
44	13	16	15	48	8	7	6
46	17	16	16	50	22	21	23
47	5	3	12	53	8	7	8
49	33	33	32	57	11	7	5
51	11	14	11	60	20	17	19
54	16	18	21				
56	8	11	15				
61	7	7	11				
63	6	4	2				

Serial 3s - Error Totals

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	0	1	0	1	0	0	0
3	2	0	0	4	0	1	0
5	1	2	0	6	0	1	0
10	0	2	0	8	1	3	0
11	0	3	2	9	1	1	0
12	0	1	0	13	0	1	0
18	1	1	0	14	2	0	0
20	0	0	0	15	2	1	1
22	0	0	0	21	0	2	0
23	0	1	1	25	0	0	0
24	1	2	0	27	0	0	1
29	0	0	0	30	0	0	0
33	0	0	0	35	0	2	0
34	0	1	0	37	4	1	1
36	0	1	0	41	1	0	0
40	1	0	0	42	0	0	3
43	3	1	4	45	0	0	1
44	1	2	0	48	1	3	2
46	0	0	1	50	0	0	2
47	1	3	0	53	0	0	3
49	0	0	0	57	1	2	3
51	0	0	0	60	0	0	0
54	1	0	0				
56	3	0	1				
61	1	0	3				
63	1	1	0				

Inglis Paired Associate Learning Test

Group 1 (Placebo-Piracetam)				Group 2 (Piracetam-Placebo)			
Subject Number	1	2	3	Subject Number	1	2	3
2	4	3	11	1	5	8	4
3	7	4	6	4	4	4	4
5	14	6	5	6	53	3	3
10	15	4	7	8	32	16	4
11	3	3	3	9	9	7	7
12	5	8	13	13	37	4	63
18	14	11	16	14	10	24	4
20	3	3	3	15	7	8	15
22	6	10	3	21	10	18	11
23	8	3	3	25	5	4	5
24	7	3	3	27	13	6	6
29	5	3	7	30	26	24	6
33	7	4	4	35	10	8	8
34	15	7	8	37	5	3	5
36	25	23	11	41	10	11	6
40	4	4	5	42	10	10	5
43	7	11	9	45	8	7	7
44	6	3	5	48	39	5	3
46	4	6	4	50	7	3	3
47	18	6	5	53	11	10	17
49	4	7	3	57	13	14	8
51	11	3	9	60	5	3	3
54	5	3	3				
56	15	13	22				
61	7	6	7				
63	12	6	3				