ALCOHOL-INDUCED PSYCHOTIC DISORDER:

A COMPARATIVE STUDY IN PATIENTS WITH ALCOHOL DEPENDENCE, SCHIZOPHRENIA AND NORMAL CONTROLS

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Dissertation submitted for the degree, Doctor of Medicine in the Faculty of

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DECEMBER 2007

DECLARATION

I, the undersigned, hereby declare that the work in this dissertation is my own original research and that I have not previously submitted it for degree purposes, in whole or in part, at any university.

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SUMMARY

Alcohol-induced psychotic disorder (also known as alcohol hallucinosis) is a complication of alcohol abuse that requires clinical differentiation from alcohol withdrawal delirium and schizophrenia. Although extensively described, few studies utilized standardized research instruments and brain-imaging has thus far been limited to case reports. The aim of this study was to prospectively compare four population groups (ie. patients with alcohol-induced psychotic disorder, schizophrenia, uncomplicated alcohol dependence and a healthy volunteer group) according to demographic, psychopathological and brain-imaging variables utilizing (i) rating scales and (ii) single photon emission computed tomography (SPECT). The third component of the study was designed to investigate the (iii) effect of anti-psychotic treatment on the psychopathology and regional cerebral blood flow (rCBF) before and after six weeks of treatment with haloperidol. Effort was made to ensure exclusion of comorbid medical disorders, including substance abuse. The study provides further supportive evidence that alcohol-induced psychotic disorder can be distinguished from schizophrenia. Statistically significant differences in rCBF were demonstrated between the alcohol-induced psychotic disorder and other groups. Changes in frontal, temporal, parietal, occipital, thalamic and cerebellar rCBF showed statistically significant negative correlations with post-treatment improvement on psychopathological variables and imply dysfunction of these areas in alcohol-induced psychotic disorder. The study was unable to distinguish between pharmacological effects and improvement acccomplished by abstinence from alcohol.

OPSOMMING

Alkohol-geïnduseerde psigose (ook bekend as alkohol hallusinose) is ‘n komplikasie van alkoholmisbruik wat kliniese onderskeid van alkoholonttrekkings-delirium en skisofrenie benodig. Alhoewel reeds omvattend beskryf, het min studies tot dusver gestandardiseerde navorsing instrumente gebruik en breinbeelding is beperk tot gevallestudies. Die doel van die studie was om vier studiegroepe (nl. pasiënte met alkohol-geïnduseerde psigose, skisofrenie, ongekompliseerde alkoholafhanklikheid en ‘n gesonde vrywilliger groep) prospektiewelik volgens demografiese, psigopatologiese en breinbeelding veranderlikes te vergelyk deur van (i) meetskale en (ii) enkel foton emissie rekenaar tomografie (“SPECT”) gebruik te maak. Die derde deel van die studie was ontwerp om die (iii) effek van anti-psigotiese behandeling op die psigopatologie en serebrale streekbloedvloei (“rCBF”) voor en na ses weke behandeling met haloperidol te ondersoek. Voorsorg was gemaak om uitsluiting van gepaardgaande mediese toestande insluitende substansmisbruik te verseker. Die studie verskaf verdere ondersteunende getuienis dat alkohol-geïnduseerde psigose van skisofrenie onderskei kan word. Statisties betekenisvolle verskille in serebrale streekbloedvloei tussen die alkohol-geïnduseerde psigose en ander groepe was aangetoon. Veranderings in frontale, temporale, pariëtale, oksipitale, talamiese en serebellêre streekbloedvloei het statisties betekenisvolle negatiewe korrelasies met na-behandeling verbetering in psigopatologiese veranderlikes getoon en impliseer disfunksie in hierdie gebiede. Die studie was nie in staat om tussen farmakologiese effekte en beterskap op grond van onthouding van alkohol te onderskei nie.

To Louisa, Juhan and Lorraine

ABBREVIATIONS

ABS - Agitated Behavior Scale

ANOVA – analysis of variance

CDS(S) - Calgary Depression Scale (for Schizophrenia)

CGI-SP - Clinical Global Impression of Severity of Psychosis

CHI – Likelihood ratio chi-square

CT – computed tomography

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

Ham-D - Hamilton Depression Rating Scale

Ham-A - Hamilton Anxiety Rating Scale

HMPAO – hexamethyl amine oxime

ICD – 10 - International Classification of Diseases, 10th edition

KW – Kruskal -Wallis

MMSE - Mini-Mental State Examination

MNI – Montreal Neurological Institute

MRI- magnetic resonance imaging

MW – Mann-Whitney

PANSS - Positive and Negative Syndrome Scale

PET- positron emission tomography

rCBF – regional cerebral blood flow

SADQ - Severity of Alcohol Dependence Questionnairre

SOF - Scale of Functioning

SPECT – single photon emission computed tomography

SUMD - Scale to assess unawareness of mental disorder

Tc-99m – technesium-99m

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1. INTRODUCTION and LITERATURE REVIEW

Alcohol-induced psychotic disorder is an uncommon but well-known psychiatric disorder. It however presents relatively frequently in the catchment area of Tygerberg Hospital in the Western Cape in South Africa.

The term “psychosis” is defined as an “inability to distinguish reality from fantasy; impaired reality testing, with the creation of a new reality” (Sadock & Sadock, 2003). It is mostly associated with delusions, hallucinations, thought process disorder and inappropriate behaviour. The most common disorders that present with psychotic features are schizophrenia, mood disorders (such as major depression with psychosis and both the manic and depressive phases of bipolar disorder), delusional disorders, psychotic disorders due to a general medical condition and substance-induced psychotic disorders.

It is known that psychotic manifestations may occur in a number of syndromes associated with alcoholism (Greenberg & Lee, 2001). In current terminology, Wernicke’s encephalopathy can be viewed as a confusional state or delirium accompanied by neurological signs, while Korsakoff’s psychosis is predominantly an amnestic (memory) disorder. Both these syndromes are regarded as different facets of the same pathologic process due to thiamine deficiency usually associated with alcoholism. Psychotic features may also be a common occurrence in alcoholic dementia similar to other dementias. Other alcohol related syndromes that may be associated with psychotic features include alcoholic pellagra encephalopathy, hepatic encephalopathy, Marchiafava-Bignami disease and central pontine myelinosis. The psychotic

features occurring in these syndromes are however predominantly associated with comorbid neurological deficits or other medical impairment and usually do not present as a distinct psychotic syndrome only.

1.1 Recognition of the Syndrome

The association between alcohol use and psychosis was documented as early as 1847 by Marcel who described “madness as a result of drinking, madness of a drunkard, drunken madness” and called it “folie d’ivrogne” (Marcel, 1847). Although Marcel has been credited for differentiating the disorder from delirium tremens (Johansson, 1961), German psychiatrists (Wernicke, 1881; Korsakoff, 1887; Ziehen, 1894 and Kraepelin, 1913) also acknowledged that some patients with alcohol dependence presented with a **distinct psychotic syndrome** that differred from delirium tremens (alcohol withdrawal with delirium), Wernicke’s encephalopathy, Korsakoff’s psychosis and alcohol-induced dementia. (Glass, 1989).

Various discriptions about the nature of and outcome of a distinct psychotic syndrome associated with alcoholism followed. Kraepelin (1913) described the disorder as follows:

“ The picture of disease which has a certain resemblance to delirium tremens, in the fantastic delusions, the vividness of hallucinations, the remarkable combination of insane ideas with a sense of illness and the alcoholic origin. It differs from delirium chiefly in its much longer duration, in the absence of any disturbance of the patients’s idea of his position, and in the predominance of

the hallucinations of hearing compared with the prevalence of hallucinations of sight in delirium tremens. The unrest, too, is generally less, and the tremors are not nearly so pronounced. For these reasons it seems best to clearly distinguish this illness from delirium tremens, although the two are certainly nearly related.....Its course may extend over several weeks or months. The outcome is generally complete recovery but there is no inconsiderable number of cases in which incurable states of weakness remain, usually with particular permanent hallucinations and delusions. " (Glass, 1989).

Bleuler (1916) termed the condition **alcoholic hallucinosis** and described the disorder in the following way:

"Alcoholic insanity is in many respects the opposite to delirium tremens. It manifests itself chiefly in auditory hallucinations, which have a peculiar character: that is they discuss him in the third person; much more rarely they speak to him. These voices threaten him also... Visions similar to those in delirium tremens may also appear intermingled with others. ...Delusions of persecution correspond to the hallucinations.....At the same time patients remain orientated and.... they generally remain clear. Attention appears to be normal.....Memory in all cases is good,.... the behaviour is proper. The dominant affect is anxiety. The patients are relatively indifferent.....suicide is not rare. Physical symptoms are insignificant. Alcoholic insanity usually breaks out very acutely. Repeated attacks are not rare. As a rule the disease passes over into recovery.....It is a question whether the delusions and hallucinations can continue to exist in a chronic form." (Glass, 1989).

These early descriptions were based on individual case-studies and clinical experience. Follow-up studies on groups of patients appeared in the literature from around the 1950's. These early descriptions as well as the studies that followed contain the core features of the syndrome which is currently known as: **Alcohol-induced Psychotic Disorder** (DSM IV, 1994) and Psychotic Disorder due to the use of Alcohol (ICD-10, 1993). (For the purpose of this discussion the term alcohol hallucinosis and alcohol-induced psychotic disorder would be used synonomously).

1.2 Description of the Syndrome

Authors generally agreed that the disorder is especially characterized by acute onset of auditory hallucinations, but also by delusions in a clear consciousness (Seitz 1951, Sokya 1988), in someone with a history of heavy drinking. The hallucinations are usually auditory in nature and typified by voices presenting unpleasant messages to the patient. The symptoms usually clear within a week, but sometimes tend to become chronic, especially in the presence of ongoing alcohol abuse (Glass 1989).

The early follow-up studies on groups of patients with alcohol hallucinosis by Benedetti (1952), Burton-Bradley (1958) and Victor & Hope (1958) did not compare their patients with patients from other diagnostic groups. Conclusions were rather formulated on grounds of their clinical observations and follow-up over a variable length of time. Since the 1960's study reports by Johansson (1961), Scott (1967, 1969), Cutting (1978), Soyka (1988, 1990)

and Tsuang (1994) utilized a more systematic research approach, comparing the onset, clinical presentation and course in patients with alcohol hallucinosis with patients with delirium tremens, schizophrenia, chronic alcoholism, toxic confusion and alcoholic paranoia.

Benedetti (1952)

He followed up 113 patients with alcohol hallucinosis over long periods, on average approximately 10 years, but some up to 41 years. All patients presented with acute onset. He documented the course of the disorder and its possible relationship to body build, family history and premorbid personality. About 30% of patients had a relapsing course and relapse occurred more often in the patients who developed a chronic illness. Interesting to note is that a minority of patients continued to experience hallucinations in spite of abstinence whilst others were resistant to relapse in spite of ongoing drinking.

He demonstrated that his patients had a varied outcome. Some patients (10%) had symptoms suggestive of a delirium in the acute phase. The majority of patients (80%) recovered within six months. Of those that remained chronic, approximately half developed schizophrenia while the other half developed a dementing illness associated with concomitant physical impairment. (Glass, 1989)

Burton-Bradley (1958)

Burton-Bradley reported on 41 patients and agreed that the majority did not resemble schizophrenia. Hallucinations cleared within one month in 35 of these patients. The appropriateness of behaviour to the hallucinatory content, absence of thought disorder and complete and rapid recovery distinguished these patients from the features usually associated with schizophrenia. It was noted that acute alcoholic hallucinosis could at the most be considered a very special subgroup of schizophrenia. Though the study supported the non-schizophrenic nature of acute alcoholic hallucinosis, the evidence was inconclusive. (Glass, 1989)

Victor & Hope (1958)

These authors followed up 70 patients over a period of approximately 5 years. Their findings supported the previous reports that alcohol hallucinosis was an acute illness with a benign course when compared to schizophrenia. The majority of their patients reflected no relationship to schizophrenia. They did however report a chronic form of the illness which occurred in 8 out of 76 cases. In four of these cases the illness could not be distinguished from schizophrenia. In three patients diagnosed with schizophrenia transient episodes of auditory hallucinations were associated with excessive drinking. Their findings also suggested that repeated episodes of hallucinosis may contribute to the development of chronic forms of the illness.

They dismissed the idea that alcohol triggered latent schizophrenia as a possible release mechanism for the development of schizophrenia. They

argued that they were unable to detect a difference in terms of age, sex, personality, alcoholic habits and mode of onset between the alcoholic patients who developed a schizophrenia-like illness and those who did not. (Glass, 1989).

Johansson (1961)

Johansson reported on 38 alcoholic patients with hallucinosis and paranoid features and compared them to a group of patients with delirium tremens. She found that patients with delirium tremens were older and had longer alcohol histories compared to those in the hallucinosis group. Patients with delirium tremens seemed to be slightly better equiped socially and intellectually, whilst the hallucinosis group had significantly more often head injuries. Johansson reported that the onset of illness in the hallucinosis group was significantly higher than the average age of onset of a previous group of patients with schizophrenia. She also confirmed the acute onset, brief duration and comparatively good prognosis of patients with alcohol hallucinosis. (Glass, 1989).

Scott (1969)

Only six of the 33 patients in this study, in which some patients were followed up for up to 17 years, represented the acute illness and good outcome that were described by other authors. These six patients had hallucinations that lasted 8 weeks or less. Seventeen patients were diagnosed as as having other diagnoses such as manic-depressive illness, schizophrenic illness,

personality disorder and drug addiction during the course of the follow-up period. This obviously makes any results difficult to interpret. (Glass, 1989).

Cutting (1978)

This retrospective study studied the nature of alcoholic psychosis through case notes of 114 patients diagnosed as alcoholic psychosis over a period of 27 years. Patients with Korsakoff's syndrome and alcoholic dementia were excluded from this group. Patients were divided into 6 diagnostic categories namely alcoholic hallucinosis (40%), delirium tremens (21%), alcoholic psychosis unspecified (18%), toxic confusion (7%), alcoholic paranoia (6%) and a mixed group "alcoholic hallucinosis? schizophrenia".

Further episodes of illness occurred in 26 of the 46 patients diagnosed with alcohol hallucinosis. Nine of the 46 patients were lost to follow-up. Of the remaining patients, 10 patients (27%) remained well and one remained unchanged. Only 7 patients (19%) presented with a further episode of alcoholic hallucinosis, 8 patients (22%) were diagnosed with affective illness, 4 patients (11%) with schizophrenia and 2 patients (5%) committed suicide. Two patients (5%) returned with delirium tremens, two patients (5%) with a paranoid psychosis and in one patient the nature of the alcoholic psychosis was unknown. Given these figures, it is evident that the diagnosis of alcoholic hallucinosis remained unchanged in at least 17 (46%) of the patients originally diagnosed with alcoholic hallucinosis. The significance of this study however therefore lie in the varied outcome that was demonstrated.

Soyka (1988, 1990)

These retrospective studies compared psychopathology in patients diagnosed with alcohol hallucinosis to those with delrium tremens (1988) and paranoid schizophrenia (1990) respectively. The **first study (1988)** examined the case histories of 154 patients with alcoholic psychosis: 103 patients with alcohol withdrawal delirium and 51 patients with alcohol hallucinosis. All the patients with clouding of consciousness and disorientation were diagnosed as alcohol withdrawal delirium, while those with a clear sensorium were diagnosed as alcohol hallucinosis. No significant differences between the two groups were reported with regard to mean age or sex ratio. When comparing psychopathology, the alcohol hallucinosis group scored significantly higher than the alcohol withdrawal delirium group on the following: delusions of reference (33.3% vs 12.6%, $p<0.01$), delusions of persecution (60.8% vs 36.8%, $p<0.01$), verbal hallucinations (84.3% vs 38.8%, $p<0.001$), and anxiety (80.3% vs 60.2%, $p<0.05$). The alcohol withdrawal delirium group scored significantly higher than the alcohol hallucinosis group on visual hallucinations (74.7% vs 29.4%, $p<0.001$). Delusions occurred in both groups, but were generally more common in the alcohol hallucinosis group.

Depressed mood (33.9% vs 39.2%) and suicidal tendencies (7.7% vs 17.6%) were common to both alcohol withdrawal delirium and hallucinosis groups respectively, and did not show statistical difference. Only patients with alcohol hallucinosis tried to commit suicide though.

The authors concluded that the two conditions have a distinct association with chronic alcoholism, but that it differs with regard to a number of psychopathological aspects as well as to the onset and course. Alcohol withdrawal delirium usually starts after 2-4 days of cessation of drinking. The onset and course of alcohol hallucinosis are difficult to predict. Clinical differentiation is important because the management of the two disorders differ.

The **second retrospective study (1990)** included a comparison of the psychopathology, family histories and individual psychiatric histories of a group of 53 patients with alcohol hallucinosis with an age- and sex-matched control group of 53 patients with paranoid schizophrenia. Patients were diagnosed according to ICD-9 and DSM-III. Patients with schizophrenia and a history of alcohol or drug abuse and patients with "organic mental disorders" were excluded from the study.

Although formal thought disorders were observed in both groups of patients, the reported frequencies were generally low (< 35%). The only exception was one item of thought disorder namely "incoherence" which occurred significantly more often in the schizophrenia than in the alcohol hallucinosis group (43% vs 17%; $p<0.01$).

No significant differences were observed with regard to disorders of affect such as anxiety (77% vs 71%), depressed mood (47% vs 54%) and blunted affect (24% vs 28%) in the alcohol hallucinosis and schizophrenia groups

respectively. Affective rigidity ($p<0.05$), ambivalence ($p<0.001$), and suspiciousness ($p< 0.001$) were reported more often in patients with schizophrenia.

With regard to disorders of perception, it is interesting to note that all the patients with alcohol hallucinosis experienced verbal (auditory) hallucinations (100% vs 83%;$p<0.01$) compared to patients with paranoid schizophrenia. Auditory hallucinations often occurred in the context of threatening or accusatory voices. Hallucinations in other sensory modalities such as vision (43% in alcohol hallucinosis vs 34% in schizophrenia groups), did not significantly differ between the groups.

Delusions generally occurred in both groups but delusions of persecution (88% vs 71%;$p<0.05$) and delusions of reference (77% vs 45%;$p<0.01$) were more commonly reported in the schizophrenia group.

Disorders of ego were the most distinct psychopathological disturbance that differed between the groups. No ego disturbances were reported in 70% of alcohol hallucinosis patients vs 13% in patients with schizophrenia ($p<0.001$). When comparing the schizophrenia group with the alcohol hallucinosis group, thought broadcasting (35% vs 13%;$p<0.01$), thought insertion (20% vs 3%;$p<0.01$) and feelings of alien influence (64% vs 24%; $p<0.001$) all occurred significantly more in patients with schizophrenia.

The family histories of the patients with alcohol hallucinosis and paranoid schizophrenia indicated that first-degree relatives of patients with schizophrenia were more commonly diagnosed with schizophrenia compared to the first degree relatives of patients with alcohol hallucinosis (20% vs 2%; $p<0.001$). Likewise the first-degree relatives of patients with alcohol hallucinosis were more likely to have an alcohol history compared to the first degree relatives of patients with schizophrenia (39% vs 2%; $p<0.001$).

Patients with schizophrenia first developed psychotic symptoms earlier than patients with alcohol hallucinosis (mean age: 32.8 vs 37.4 years). Patients with alcohol hallucinosis had a more favourable outcome to those with schizophrenia. On discharge, 85% of patients with alcohol hallucinosis and 55% of patients with schizophrenia were reported to be symptom-free.

In conclusion, it was clear that paranoid and hallucinatory symptoms are frequent occurrences in both alcohol hallucinosis and paranoid schizophrenia. The results however support the notion that the two disorders can be distinguished with regard to other psychopathological features such as disorders of ego, family history, age of onset and prognosis.

Tsuang (1994)

This study was designed to evaluate the characteristics of male patients with a history of alcohol hallucinosis whose illness was independent of major psychiatric disorder or other drug use. A group of patients with a history of alcohol hallucinosis (n=48) was compared with a group of alcoholic patients

(n=484) without a history of hallucinations. No significant differences on demographic data such as age, educational level, marital status or employment were found between the groups. Patients with a history of alcohol hallucinosis were significantly younger at their age of first occurrence of major problems related to alcohol. They also reported a higher average and greater maximum quantity of alcohol drinks per day. Their lifetime drug consumption history indicated that patients with alcohol hallucinosis had higher rates of drug experimentation and higher mean number of drugs used. Interestingly, a higher percentage of men with alcoholic hallucinosis had histories of depression lasting more than 2 weeks. First degree relatives with histories of schizophrenic disorders were similarly represented in both groups, supporting the view that alcohol hallucinosis is independent of a schizophrenic syndrome.

1.3 Controversial Issues relating to the Diagnosis.

It is interesting to note that not all authors agreed to the concept of a distinct syndrome caused by alcohol. Controversy about the nature of the disorder has characterized the literature and endured for many years (Glass, 1989). The controversy mainly revolves around etiological and phenomenological aspects concerning the disorder. These uncertainties include: whether hallucinations other than auditory are present, whether consciousness is always clear, whether orientation is completely intact, whether there are signs of cognitive impairment and what the natural course of the disorder entails.

Henderson & Gillespie (1936) suggested that similar hallucinoses could occur in the absence of alcoholism. Schneider (1928) was of the opinion that patients who developed alcohol hallucinosis tended to be manic-depressive, while Suwaki et al (1976) also suggested the possible association with **mood disorders** such as depression with paranoid features. May & Ebaugh (1953) considered it to be a schizophrenic reaction precipitated by alcohol and therefor a “waste-paper basket category”.

Huber (1939) suggested two forms of alcohol hallucinosis namely one with a delirium tremens component and one with a schizophrenia component. It was however postulated that alcohol hallucinosis is an independent syndrome that could indirectly precipitate a latent form of schizophrenia. The studies of Benedetti (1952), Scott (1967, 1969) and Cutting (1978) (discussed earlier) also pointed towards a varied outcome.

Most of the controversy can however be attributed to the nature of the disorder whose symptomatology overlaps with that of delirium tremens (alcohol withdrawal with delirium) and with schizophrenia. Alcohol induced psychotic disorder has to be distinguished from alcohol withdrawal delirium (Sokya 1988, Gross 1968, Sobczyk 1983), other psychotic disorders such as schizophrenia (Glass 1989, Soyka 1990), psychoses associated with epilepsy (Slater et al, 1963, Roberts et al , 1990, Nicolson et al 2007) and head injuries (David & Prince, 2005).

1.3.1 Association with Alcohol Withdrawal Delirium "Delirium Tremens"

The classic **alcohol withdrawal delirium** ("delirium tremens") can present similarly and many authors have assumed a close relationship between the two disorders. Various descriptions have been documented eg. "systematized pattern of delusions in a delirium of an alcoholic type" and "alcoholic delirium of an auditory type". Kraepelin believed that delirium tremens and alcoholic hallucinosis were related features of the same process. He however pointed out that the course of the disorder was shorter in delirium tremens and that the hallucinations were more likely visual than auditory. He also acknowledged the possibility of a more chronic course in alcohol hallucinosis which ought to be differentiated from schizophrenia. Bowman & Jellinek (1941), likewise, noted the longer duration of alcoholic hallucinosis. They supported the observation that patients with alcoholic hallucinosis were usually orientated with intact attention and free of psychomotor agitation. They were also of the opinion that patients with alcohol hallucinosis had more introverted personalities and their family histories were more suggestive of psychiatric illness than those patients with delirium tremens.

In investigating etiological factors, Scott (1967), found no differences in the marital, occupational and social status amongst 3 groups of patients diagnosed with alcoholic hallucinosis, chronic alcoholism without psychosis and delirium tremens. Although he stated that classical alcohol hallucinosis does not include delirious features such as disorientation, he indicated that "there are some cases in which delirious features are present".

Gross et al (1968,1970,1972a,1972b) challenged the distinction between alcoholic hallucinosis with a clear sensorium and delirium tremens with visual hallucinations and clouding of consciousness. They proposed a spectrum of acute hallucinatory states allowing for mild clouding of consciousness in alcoholic hallucinosis.

Soyka et al (1988) addressed this issue extensively (as discussed in the previous section) and concluded that the two disorders can be distinguished clinically. The most important criteria of demarcation were clouding of consciousness and disorientation which were present in all patients with alcohol withdrawal delirium. Visual hallucinations were found significantly more in patients with alcohol withdrawal with delirium as opposed to auditory hallucinations which were significantly more common in the patients with alcoholic hallucinosis.

1.3.2 Association with Schizophrenia

The distinction from **schizophrenia** (especially paranoid schizophrenia) is also historically controversial, in view of the fact that alcohol hallucinosis may be difficult to clinically distinguish from (i) schizophrenia with secondary alcohol dependence ("self-medication hypothesis"). Other considerations are that alcohol hallucinosis is (ii) a latent form of schizophrenia precipitated by alcohol, (iii) a psychotic disorder that arises as a direct toxic effect of alcohol or (iv) a coincidental occurrence of schizophrenia in someone with a history of chronic drinking.

The possibility that alcohol could act as an independent etiological agent in the development of a specific psychosis was initially dismissed by many authors. Bleuler was of the opinion that alcoholic hallucinosis could be a syndrome of schizophrenia induced by alcohol. Bleuler accepted that disorders of thought and language as well flattening of affect were central to the diagnosis of schizophrenia. The notion of alcoholic hallucinosis as a latent form of schizophrenia was prominently received in the literature in spite of the relative absence of these symptoms in alcohol hallucinosis. Davidson (1939) was of the opinion that alcoholism and the hallucinosis both reflected symptoms of an underlying schizophrenia.

As mentioned earlier in this section, the studies by Burton-Bradley (1958) and Victor & Hope (1958) supported the non-schizophrenic nature of alcohol-induced psychosis. Surawicz (1980) pointed out that: “Alcoholic hallucinosis differs from schizophrenia in several respects including age, family history, duration, premorbid personality, affect and the absence of formal thought disorder.” The study by Soyka (1990) (see previous section) supported the existence of alcohol hallucinosis as a disorder independent of schizophrenia.

Glass (1989) in her comprehensive review on the subject was struck by the lack of consistency in the diagnostic criteria for alcohol hallucinosis at that time. The articles by Soyka et al (1988, 1990) were published before and after her review and thus probably both not available at the time of the review.

The distinction from alcohol withdrawal delirium and schizophrenia is clinically relevant, because the management and prognosis differ from that of alcohol induced psychotic disorder. Alcohol-induced psychotic disorder is an indication for anti-psychotic treatment. Hallucinations and delusions usually clear within a few days to weeks with anti-psychotic treatment. Alcohol free patients then usually do not require further neuroleptic treatment and the prognosis is usually good.

Sometimes alcohol-induced psychotic disorder is incorrectly diagnosed as schizophrenia and these patients then receive unneccesary anti-psychotic treatment for indefinite periods (Soyka 1990). Schizophrenic patients with co-morbid alcohol abuse and/or dependence often contribute to diagnostic and therapeutic uncertainty. Clinical markers assisting in early distinguishing between the two disorders, would therefor also be beneficial in the introduction of appropriate management and avoiding of unneccesary treatment. The similarites and differences between alcohol induced psychosis and schizophrenia is a rich topic for comparative research between the two disorders.

One aspect that may assist in the quest to distinguish the pathogenesis and neurobiology of the two disorders is the presence of positive (present) and negative (absent or deficit) symptoms that have been described in schizophrenia (Strauss et al 1974). Crow (1980) postulated that these positive symptoms represent a hyperdopaminergic state whilst the negative

symptoms reflect structural brain-deficit in schizophrenia. Prodromal and residual symptoms seem to coincide with the negative syndrome in schizophrenia but appear to be relatively infrequent in alcohol-induced psychotic disorder. The Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987) was consequently developed and provides a valuable clinical and research instrument to explore the psychopathology of schizophrenia. Several studies have assessed the factorial validity of the PANSS in schizophrenia (Emsley et al, 2003). Not only did the negative and positive symptoms emerge as distinct components, but three addtional components have subsequently emerged. Current thinking favours a five factor structure for schizophrenia consisting of positive (p1,p3,p5,p6,g9,g12), negative (n1,n2,n3,n4,n6,g7,g13,g16), disorganized (p2,n5,n7,g5,g10,g11,g15), excitement (p4,p7,g8,g14), and depression/anxiety (g1,g2,g3,g4,g6), factors. (See table 4 and table 6). Furthermore, the occurrence of positive and negative symptoms as described in schizophrenia has not been investigated in alcohol-induced psychotic disorder.

1.4 Lack of Standarized Research Methods:

Another reason for the controversy lies with the lack of standardized research methods used to explore the nature of the disorder. Past studies have mainly dealt with descriptive aspects including the natural course and the possible contributing genetic factors concerning the development of the disorder (Benedetti 1952, Burton-Bradley 1958, Victor & Hope 1958, Johansson 1961, Scott et al 1967, Cutting 1978 & Soyka, 1988, 1990).

It is evident (Glass 1989), that standardised interviews and rating scales including reliability data for the evaluation of personal history, alcohol history, premorbid personality, medical history and mental status examination were lacking during initial and subsequent assessments for most studies. Most information was collected from clinical notes. It is readily understood that the descriptive case histories that appeared in the literature utilized different inclusion and exclusion criteria making comparison difficult. Biochemical and hematological investigations, urinary toxicological screening and psychological testing were documented in few studies. Brain imaging was probably not available for most investigators.

There is therefore a need for standardized documentation of alcohol induced psychosis along with the use of tecnological instruments (eg. brain imaging) that have thus far not been systematically researched in this disorder. Currently, standardised psychiatric rating scales such as the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) as well as technological measures such as Single Photon Emission Computed Tomography (SPECT) are available. According to Soyka (1990), research on biological aspects of brain function and morphology in alcohol induced psychosis could also contribute to develop a better understanding of the biological underpinnings of schizophrenia.

1.5 Etiology of the Syndrome

Increase in central dopaminergic activity, subsensitiviy of the dopamine receptor (Borg et al, 1986: Fadda et al, 1989; Soyka, 1993), serotonin

dysfunction (Soyka, 1993, 1997; Branchey et al, 1985), altered beta-carboline activity (Rommelspacher et al, 1991), involvement of essential fatty acids (Glen et al, 1989) and possible damage to auditory and sensory pathways (Spitzer, 1981), have all been investigated as possible mechanisms for the development of hallucinations in patients with alcoholism. Although a variety of different hypotheses have been suggested, none have thus far been able to explain the occurrence of psychotic symptoms in patients with alcoholism. (Soyka, 1995)

Genetic studies have mainly contributed to distinguishing alcohol hallucinosis from schizophrenia. Brain-imaging remains a promising but relatively underutilized research technique available to unravel the pathogenesis of this disorder These strategies will briefly be discussed below.

1.5.1 Genetic Studies

There is substantial evidence that genes play a role in the development of alcoholism. It is also widely accepted that a single or a few genes are unlikely responsible for the vulnerability to alcoholism. Family, twin and adoption studies have been utilized to explore the relationship between alcohol hallucinosis, alcoholism, delirium tremens and schizophrenia. Four of the follow-up studies mentioned earlier, studied the famliy histories of patients with alcohol hallucinosis.

Benedetti, Victor & Hope and Johansson reported a higher incidence of alcoholism in the families of patients with alcohol hallucinosis than in the

general population. Benedetti also found a family history of schizophrenia in relatives of patients with alcohol hallucinosis to be more common than in the general population, but less common than in relatives of patients with schizophrenia. This was different to Scott et al who reported a similar incidence in schizophrenia in the relatives of patients with alcohol hallucinosis to that in the general population. Schuckit and Winokur (1971) could not distinguish patients with alcohol hallucinosis (n=61) on grounds of a prior history of schizophrenia in or a higher incidence of schizophrenia in their families when comparing them with a group of alcoholic patients without hallucinosis. Likewise Schuckit (1982) again reported no association between the psychotic symptoms in alcoholic patients (n=220) and a personal or family history of schizophrenia.

Kendler et al (1985) reported that alcoholism is significantly less common in first degree relatives of patients with schizophrenia than in the relatives of controls. In a twin study, Kendler (1985) found that schizophrenia and alcoholism alone and in combination were more common in monozygotic than in dizigotic twins. This suggests that patients with alcoholism and schizophrenia have a predisposition to each disorder separately.

Kendler further reported that alcoholic psychosis was significantly more common in monozygotic (32%) than dizygotic (13%) index twins. He also reported no significant difference in the frequency of schizophrenia or alcoholism in the co-twins of index twins, with or without a diagnosis of alcoholic psychosis.

Soyka (1990) (see earlier text) demonstrated that patients with schizophrenia significantly more often reported a positive family history for schizophrenia compared to patients with alcohol hallucinosis who were significantly more likely to have a positive family history for alcoholism.

Hrubec & Omenn (1981) reported on the concordance for alcoholism (26.3% vs. 11.9%), alcoholic psychosis (21.1% vs. 6%), and liver cirrhosis (14.6% vs. 5.4%) in monozygotic and dizygotic twins respectively. These results support a genetic predisposition for and separate transmission of organ specific vulnerabilities to alcohol damage.

In summary, Glass, (1989b) concluded that these studies do not support a genetic predisposition to schizophrenia in patients with alcohol hallucinosis. More likely, these results rather suggest a genetic vulnerability to the psychotogenic effect of alcohol in some patients with alcoholism and lends further support to the concept of alcohol-induced psychotic disorder as an independent disorder.

1.5.2 Brain Imaging Studies

1.5.2.1 Neuroimaging in Alcoholism

Although regional cerebral blood flow (rCBF) increases in most brain areas during acute alcohol intake in normal individuals (Newlin 1982), early studies generally showed decreased flow in gray and white matter areas in subjects with chronic alcoholism and alcohol amnestic disorder (Rogers et al., 1983, Meyer et al 1985, Ishikawa et al., 1986) Most SPECT neuroimaging studies

have shown reduced cerebral and particularly decreased frontal lobe blood flow in alcohol dependence as reviewed by Moselhy et al (2001). SPECT studies by Melgaard et al (1990) and Nicolas et al (1993) reported that hypoperfusion was significantly correlated with impaired neuropsychological performance in patients with alcoholism. Frontal hypoperfusion in chronic alcoholics did however not necessarily correlate with cortical atrophy as determined by computerized tomography (CT), because impaired rCBF was also demonstrated without atrophy (Erbas et al, 1992). Nicolas et al (1993) confirmed the usefulness of rCBF as a better indicator of neuropsychological function than the degree of atrophy in patients with alcoholism.

Positron emission tomography (PET) studies also supported the view that chronic alcohol intake results in impaired cerebral function particularly in the medial frontal region (Adams et al 1993) and superior medial aspects of the frontal lobes (Gilman et al 1996). Brain glucose metabolism as measured with PET recovered significantly in frontal regions during early abstinence, whereas persistent low metabolic levels were reported in the basal ganglia (Volkow et al, 1994). Similarly, George et al (1999) reported that multiple detoxifications were associated with significantly lower activity in temporal lobes and visual cortex compared with first episode patients, whilst Ishikawa et al (1986) and Gansler et al (2000) concluded that frontal brain perfusion abnormalities may subside with extended abstinence.

Berglund & Risberg (1981), using the Xenon 133 inhalation method and Caspari et al (1993), using SPECT with technesium-99-HMPAO, reported

heterogeneous regional activity in patients with alcohol withdrawal. Increased functional activity in portions of the temporal cortex with decreased functional activity in other portions of the temporal and parietal cortex were reported**.** Furthermore, Bartsch et al (2007) reported spatially significant brain volume gain around the superior vermis, perimesencephalic, periventricular and frontal brain edges in patients after short-term (6-7weeks) sobriety from alcoholism, utilizing MR morphometry along with metabolic and neuropsychological indicators. These findings were not attributed to rehydration only, but implied metabolic as well as morphological (especially white matter) partial recovery from the toxic effects of alcoholism.

1.5.2.2 Functional Neuro-imaging in Alcohol-induced Psychotic Disorder

Information concerning brain imaging in alcohol-induced psychotic disorder is limited and mainly consists of case reports. To date, we are not aware of any longitudinal studies utilizing clinical correlates and functional neuroimaging in alcohol-induced psychotic disorder.

Soyka et al (2000a, 2000b, 2005) reported Fluorodeoxyglucose (FDG) PET data in four patients suffering from alcohol hallucinosis that suggest possible thalamic dysfunction in this syndrome. Glucose metabolism was reduced in both frontal regions (28-30%), both thalamic regions (50%) and cerebellum (36%) of one patient (Soyka et al 2000a). In the other patient the right thalamus demonstrated less (10-18%) FDG uptake than the left thalamus (Soyka et al 2000b). Soyka et al (2005) also described marked left-to-right and right-to-left assymmetry showing hypometabolism in both thalamic

regions in two other patients with alcohol hallucinosis. Improvement of right thalamic metabolism was demonstrated 4 weeks later in the symptom-free abstinent patient.

Kitabayashi et al (2007) reported decreased rCBF in the frontal lobe, left basal ganglia and left thalamus of a 56-year old patient with alcohol-induced psychotic disorder prior to treatment, using N-isopropyl-p-^{123}I iodoamphetamine (^{123}I-IMP) single photon emission computed tomography (SPECT). After treatment with diazepam and haloperidol (6mg/day) and subsequent disappearance of hallucinations, the rCBF normalized in the left basal ganglia and left thalamus, but decreased flow in the frontal lobe remained. These findings suggest that hypofrontality may represent the long-term effects of alcohol dependence whilst normalization of rCBF in the left thalamus and left basal ganglia could represent dysfunction in these areas that may be associated with the development of alcohol-induced psychotic disorder.

1.5.2.3 Brain Imaging in Schizophrenia

Lateral and third ventricular enlargement and cortical volume reduction of the brain as shown on Computed Tomography (CT) of the brain in patients with schizophrenia have been well documented and provided some of the earliest evidence that schizophrenia is a brain disease. (Weinberger et al, 1979a, 1979b, 1982). Magnetic Resonance Imaging (MRI) has shown that the volumes of the amygdala complex and parayhypoccampal gyrus of the temporal lobe are also reduced in patients with schizophrenia (Bogerts et al,

1993). In a meta-analysis review by Honea et al (2005), only two areas of the 50 areas where volume deficits were reported in schizophrenia, reported deficits in more than 50% of the 15 investigated morphometric studies. These areas were the left superior temporal gyrus and the left medial temporal lobe. Longitudinal studies have also reported progressive brain volume loss in patients with schizophrenia. These changes appeared to be particularly evident in the frontal lobes (Ho et al, 2003, DeLisi et al, 2006).

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography studies have demonstrated both impairment (hypofrontality) (Brodie et al 1984, Wolkin et al 1985, Lewis et al 1992, Andreasen et al 1992) and increase (hyperfrontality) (Volkow et al 1986, Wiesel 1987, Szechtman et al 1988, Catafau et al 1994) of frontal regional cerebral blood flow (rCBF) and regional glucose metabolism in patients with schizophrenia (Sabri et al, 1997). Similarly inconsistencies were reported from studies that demonstrated increased (Brodie et al 1984, Wolkin et al 1985) and decreased (Sheppard et al 1983) metabolism in the basal ganglia. Hypoperfusion of the temporal lobes were reported in a number of studies (Crow 1990, Paulman et al 1990, Catafau et al 1994) especially of the left temporal lobe (Klemm et al 1996).

Studies that investigated the correlation of regional cerebral blood flow abnormalites with psychopathology in schizophrenia revealed interesting results (Gur et al 1995; Erkwoh et al 1999). Statistically significant correlations were found between negative symptoms of schizophrenia and left frontal hypoperfusion and between positive symptoms and left temporal

hypoperfusion (Liddle et al 1992 Klemm et al 1996). Of particular interest are the studies that investigated the correlation between hallucinations and rCBF. Silbersweig et al (1995) reported a number of areas associated with increased brain activity and auditory hallucinations. These areas included the thalamus (bilateral), the right putamen and the left parahippocampal gyrus. Hallucinations also correlated negatively to regional cerebral blood flow to the left thalamus in never treated patients with acute schizophrenia (Sabri et al, 1997).

Some of the observed changes are not necessarily specific for schizophrenia and similar changes have been reported in other neuropsychiatric disorders. Substance abuse is one factor that needs to be considered as being responsible for some of the brain changes seen in schizophrenia studies. Studies that excluded subjects with substance abuse, were however consistent with brain imaging findings in other schizophrenia studies. (DeLisi, 1999).

Brain imaging often has limited value in the diagnostic workup of patients presenting with psychosis. Clinically it is however often useful to rule out structural brain lesions associated with general medical condtions. It may also provide supportive evidence in patients presenting with schizophrenia. Notwithstanding its current clinical limitations, brain imaging is an invaluable in vivo research tool in neuropsychiatry.

1.6 Summary of Current Knowledge of the Syndrome

Although Glass (1989) concluded that there is no concensus view relating to the nature of the disorder, she acknowledged that it does exist. Both DSM IV and ICD-10 have diagnostic categories that accept the existence of the disorder. (See Appendix A and Appendix B).

1.6.1 Etiology

The relationship of this disorder with the degree of alcohol dependence, physical impairment and cognitive dysfunction is uncertain.

Evaluation of familial and genetic factors showed that psychotic symptoms in alcohol dependent individuals are unlikely related to a genetic predisposition to schizophrenia. This corresponds to Cutting's opinion that alcohol induced psychosis should be viewed as a general medical related disorder rather than functional psychosis such as schizophrenia. A further conclusion is that the vulnerability of certain alcohol dependent individuals to the development of psychosis is probably genetically determined. No studies have thus far been able to explain the development of psychotic symptoms in patients with a history of alcoholism.

1.6.2 Epidemiology

In South Africa the proportion of the population using alcohol was found to be low (44.7% men; 16.9% women) in comparison with most developing countries. Life-time alcohol related problems were however reported as substantial (27.8% men ; 9.9% women) and many of those that drink reported

risky drinking especially over weekends (32.8% men; 32.4% women) (Parry, 2005).

Unfortunately the epidemiological data for alcohol-induced psychotic disorder are limited. No local figures are available. Whereas the lifetime risk for alcohol dependence is 10-15% for males and 3-5% for females Schuckit (2005), only about 3% of patients with alcoholism have auditory hallucinations or paranoid delusions associated with heavy drinking or withdrawal. These figures however do not exclude patients with alcohol-withdrawal delirium. It is estimated that the alcohol-induced psychotic disorder patients represent a minority of this group (Soyka, 1988). It may however also be possible that a percentage of patients with alcohol-induced psychotic disorder receive other diagnoses eg. “dual diagnosis”, alcohol-withdrawal delirium etc. which may imply underreporting of this disorder.

1.6.3 Clinical Presentation

DSM IV specifies that the onset of symptoms should be within a month of alcohol intoxication or withdrawal. The most common symtoms are auditory hallucinations, usually in the form of derogatory or threatening voices, delusions, often of a paranoid nature accompanied by anxiety. These may be associated with suicidal behaviour, with or without depressive features. Symptoms occur in a clear sensorium. Reality testing is usually impaired during the acute episode and most people regain insight after the hallucinations have subsided. Symptoms may occur at any age, but more often in patients who have abused alcohol for a long time.

1.6.4 Management

Patients who develop alcohol-induced psychotic disorder usually require hospitalization, often due to the risk of suicide. The disorder is an indication for the use of anti-psychotic medication. However, no clinical trials have objectively assessed their efficacy.

1.6.5 Course & Prognosis

The initial episode is usually acute lasting days or weeks. A chronic course may develop with exacerbations increasing in frequency. Abstinence from alcohol usually leads to remission, but not neccesarily. The risk of relapse is thus high in the presence of ongoing abuse. Generally the prognosis is however better than that of schizophrenia. (Soyka, 1990)

1.7 Problem Statement

As mentioned earlier, there is concensus in the literature that alcohol-induced psychotic disorder exists as a separate entity. Although much has been reported about the phenomenological aspects of psychopathology, very little has been reported about the pathogenesis and neurobiology. This include limited availability of neuro-imaging case reports and to our knowledge no documented neuro-imaging studies. Case reports have suggested decreased metabolism in cortical and subcortical brain areas with specific involvement of the thalumus, basal ganglia and frontal lobes in patients with alcohol-induced psychotic disorder (Soyka et al 2000a, 2000b, 2005 and Kitabayashi et al 2007). Neuroimaging of the brain in patients with alcohol dependence suggests reduced regional cerebral blood flow in the frontal and temporal

lobes (reviewed by Moselhy et al, 2001). Furthermore, many reports on alcohol-induced psychotic disorder have lacked standardized methods and/or were characterized by methodological deficits.

With this background, it is evident that a prospective comparative research design with standardized research measures focussing on a combination of psychopathological and neurobiological measures would serve as a useful way of exploring the nature of this disorder. In addition, there is a need for a standardized methodological research design. In this respect, one of the needs would be to ensure relatively pure population groups under investigation. These would include specific clinical measures to rule out comorbid pathology suc as substance abuse, head injuries, neurosyphillis etc. A longitudinal repeated-measure research design that correlates psychopathology measurements with radioimaging as has been utilized in a number of schizophrenia studies would satisfy these requirements.

2. AIMS OF THE STUDY

The overall aim of this study was to prospectively investigate demographic, clinical (including psychopathological) and brain-imaging aspects in patients with **alcohol-induced psychotic disorder** and to compare these variables in comparative groups namely, patients with (ii) acute signs of **schizophrenia** (including hallucinations), (iii) uncomplicated **alcohol dependence** and (iv) **healthy volunteers.**

2.1 Objectives

Specific objectives were as follows:

First objective: To compare all four population groups ie. patients with alcohol-induced psychotic disorder, schizophrenia, uncomplicated alcohol dependence and the healthy volunteer group according to demographic and psychopatological variables (utilizing rating scales).

Second objective: To assess and compare all four population groups ie. patients with alcohol-induced psychotic disorder, schizophrenia, uncomplicated alcohol dependence and healthy volunteer group, utilizing single photon emission computed tomography (SPECT) brain-imaging.

Third objective: To investigate the effect of standard anti-psychotic treatment (haloperidol) on psychopathology and regional cerebral perfusion (as assessed by SPECT) before and after treatment with haloperidol. Clinical assessments (including PANNS and other rating scales) were performed after completion of the study (6 weeks).

2.2 Hypothesis

We postulated that:

(i) alcohol-induced psychotic disorder is a discrete clinical entity that can be differentiated from non-alcoholic, non-schizophrenic control subjects (healthy volunteers), schizophrenia and uncomplicated alcohol dependence by means of standardised clinical assessment and SPECT imaging.

We furthermore hypothesized that:

(ii) changes in regional perfusion in patients with alcohol-induced psychotic disorder would be demonstrated in the basal ganglia, thalamus, frontal and temporal lobes.

(iii) clinical and brain imaging variables of alcohol induced psychotic disorder would normalize with anti-psychotic treatment and therefore shed light on the possible correlation between clinical symptoms and neuroanatomical dysfunction.

3. METHODS

3.1 Participants

Patients with alcohol-induced psychotic disorder and schizophrenia were recruited from the acute psychiatric admission population of Stikland- and Tygerberg Hospitals. Patients with alcohol dependence were recruited from Stikland Hospital prior to entering a rehabilitation programme, whilst healthy volunteers responded to local advertisements.

Twenty-eight (n=28, F/M) patients with alcohol-induced psychotic disorder, twenty-one (n=21, F/M) with schizophrenia, twenty (n=20, F/M) with uncomplicated alcohol-dependence according to DSM criteria (American Psychiatric Association, 1994) and 19 healthy volunteers entered the baseline psychopathology component of the study. Of these 9 patients with alcohol-induced psychotic disorder and 5 with schizophrenia did not participate in the neuro-imaging-, SPECT-study component of the study. Nineteen patients with alcohol-induced psychotic disorder participated in the open treatment study component of the study.

3.2 Study Components

The **psychopathology component** of the study involved the baseline comparisons of (a) demographic and (b) general psychopatological variables amongst the four groups as outlined earlier as the first objective of the overall study. The third section (c) reports on comparative psychopathology in alcohol-induced psychotic disorder and schizophrenia utilizing the PANSS rating scale, whilst the fourth section (d) comprises analysis of

psychopathological PANSS variables pre- and post-psychopharmacological treatment.

The **SPECT study component** compared baseline SPECT variables between the four research populations namely alcohol induced-psychotic disorder, schizophrenia, alcohol dependence and healthy volunteers. Pre- and post-treatment SPECT comparisons were also made in the alcohol-induced psychotic disorder group. Of note is that SPECT comparisons between groups were directed at specific brain areas as discussed and motivated earlier. The specific areas under investigation were the frontal lobes, temporal lobes, basal ganglia and thalamus.

The **SPECT vs PANSS correlations component** of the study compared psychological PANSS ratings and functional neuranatomical SPECT variables before and after an anti-psychotic treatment period of six weeks only in patients with alcohol-induced psychotic disorder. Of note is that SPECT comparisons before and after treatment were not directed at specific brain regions as in the previous component of the study. The effect of treatment allowed for assessment of all brain regions. A threshold of $p<0.001$ was utilized as level of statistical significance.

3.3 Procedure

All participants were interviewed with the Mini International Neuropsychiatric Interview (Version 4.4) (American Psychiatric Association, 1994, Sheehan et al 1998). Patients who met critria for another active DSM IV Axis I disorder,

including recent history of other substance abuse or dependence (excluding nicotine related disorders), were excluded from the study. Patients with schizophrenia with a history of alcohol (or any substance) abuse and/or dependence and patients with complicated alcohol dependence other than alcohol–induced psychotic disorder were also excluded from the study (eg. patients with alcohol-induced persistent dementia and alcohol-induced persisting amnestic disorder.) Careful attention was therefore given to exclude patients with current alcohol-withdrawal or alcohol-withdrawal delirium in both the alcohol-dependent and alcohol-induced psychotic disorder groups.

Written informed consent was obtained from all participants after the protocol had been ethically approved by the Research Committee of the Faculty of Medicine at the University of Stellenbosch. A general physical clinical examination (including vital signs, blood pressure, pulse rate) was performed. Blood chemistry investigations, including urea and electrolytes, liver function tests, random glucose, full blood count and serology for syphilis were performed in the healthy volunteer group and where clinically indicated in the other groups. Urine sampling was randomly performed for alcohol and toxicological screening in all groups. Patients who had clinical significant medical or neurological disorders (including epilepsy and history of head injury) were excluded from the study. Women (of child bearing age) were assessed for pregnancy and those with confirmed pregnancy and lactating mothers were not entered into the study. Patients were free to withdraw at any time during the course of the study.

All patients were required to undergo MRI scanning of the brain at the Magnetic Resonance Centre of the Christiaan Barnard Memorial Hospital, Cape Town, mainly to exclude major structural brain lesions. This is a non-invasive, radiation free procedure. Axial T2-weighted imaging was performed. If abnormal, these were followed by a fluid attenuated inversion recovery sequence (FLAIR). MRI assessments were primarily utilized to exclude patients with clinical significant comorbid neurological conditions (such as space occupying or vascular lesions, eg infarcts) that would have required independent clinical intervention. Cortical atrophy was not an exclusion critrion unless accompanied by clinical significant cognitive impairment. These assessments were not compared as part of the study.

Participants who used any psychotropic medication during the 10 days prior to the study (including alcohol and excluding benzodiazepines and/or cigarette smoking), or required psychotropic medication during the course of the treatment study other than benzodiazepines, haloperidol and benzhexol (anti-cholinergic agent) were excluded from the study. A maximum of 4mg/day lorazepam equivalent was allowed during the treament study.

3.3.1 Rating scales and clinical research instruments (See Appendix E)

The following clinical research instruments were utilized and/or performed in all patient groups except where stated otherwise:

Agitated Behavior Scale (ABS)

This scale developed by Corrigan for assessment of agitated patients with traumatic brain injury was used in the alcohol-induced psychotic disorder and schizophrenia groups. It has shown relative stability across samples of different diagnostic groups and has subsequently been utilized in schizophrenia studies. (Corrigan, 1989)

Calgary Depression Scale for Schizophrenia (CDSS)

The Calgary Depression Scale was designed for the assessment of depression in schizophrenia. It has been reported to be reliable and valid and does not overlap with negative or extrapyramidal symptoms. (Addington et al,1993)

Clinical Global Impression of Severity of Psychosis (CGI-SP)

This is a 7-point scale reflecting global impression of severity of psychotic illness and was performed in the alcohol-induced psychotic disorder and schizophrenia groups. (Guy, 1976).

Hamilton Depression Rating Scale (Ham-D)

This scale measures the degree of clinical depression. (Hamilton, 1960)

Hamilton Anxiety Rating Scale (Ham-A)

This is a scale for measuring the degree of anxiety. (Hamilton, 1959)

Mini-Mental State Examination (MMSE)

The mental status examination is a well established screening method for cognitive impairment. (Folstein et al, 1975)

Positive and Negative Syndrome Scale (PANSS)

This standardized rating scale developed as research instrument in schizophrenia was the primary clinical measure of psychosis in the alcohol-induced psychotic disorder and schizophrenia groups in this study. The 30 – item scale consists of seven items on a Positive subscale, seven items on a Negative subscale and the remaining 16 on a General Psychopathology subscale. The PANSS is scored by adding the ratings for each subscale as well as summation of ratings accross subscales to determine a total score. (Kay et al, 1987)

Scale of Functioning (SOF)

This is a well validated 15-item scale assessing multi-dimensional social functioning in areas such as particiapation in structured activities, socialization and financial management in patients with schizophrenia. (Rapaport et al, 1996)

Scale to assess unawareness of mental disorder (SUMD)

A subset of 6 items of this multidemensional scale was used to assess insight into illness in the the alcohol-induced psychotic disorder and schizophrenia groups: This scale has been reported to be a reliable and valid research instrument especially in patients with schizophrenia. (Amador et al, 1993)

Severity of Alcohol Dependence Questionnairre (SADQ)

This 27-item self-report questionnairre was utilized to assess severity of alcohol dependence in the two alcohol groups. Results have indicated that the SADQ is a reliable and valid instrument for the assessment of the degree of alcohol dependence. (Stockwell et al, 1979, 1983).

3.3.2 Functional Brain Imaging (SPECT)

All patients (including the age matched healthy volunteer group) underwent single photon emission computerized tomography (SPECT) at the start of the study. The **alcohol-induced psychotic disorder** group had a similar SPECT study after completion of 6 weeks of haloperidol treatment. SPECT of the brain, using the functional brain imaging agent technetium-99m (Tc-99m) **hexamethyl amine oxime (HMPAO)** was performed according to a standardised protocol, routinely used at our institution.

Tc-99m HMPAO is a highly lipophilic substance, which rapidly crosses the blood-brain barrier to be taken up by the neurones. The neuronal uptake is directly proportional to regional cerebral blood flow (rCBF) over a wide range of flow rates. It has been shown that rCBF is directly related to regional

cerebral metabolic rate (Sokoloff L, 1981). After the substance enters the neurones it is converted to a hydrophilic substance, which is then trapped within the neurones. Subsequent imaging of the distribution of the radioactive tracer in the brain provides information about regional cerebral blood flow and, indirectly, about regional cerebral metabolism.

3.3.2.1 Patient preparation

An intravenous cannula was placed in an arm vein and a solution containing 200mg sodium perchlorate was administered orally to minimise uptake of free pertechnetate by the salivary glands. Patients then remained comfortably in the supine position with their eyes open in a quiet, dimly lit room for 30 minutes. This was done to achieve a basal cerebral metabolic state. After completion of the 30 min rest period, a dose of 555 MBq of Tc-99m HMPAO was injected through the intravenous cannula. The patients were then required to remain in the resting state for a further 10 min to allow for uptake of the radiopharmaceutical in the brain.

3.3.2.2 Data acquisition

Patients were required to lie completely still on the imaging table, in the supine position, with the head supported by a headrest. The patient's head was lightly strapped to the headrest to ensure absence of head movement during data acquisition. SPECT imaging then commenced employing a standard clinical imaging protocol, using a dual detector gamma camera (Elscint Helix, GE Medical Systems,USA) equipped with fan beam

collimators. Data were acquired utilising a circular orbit through 360° with the camera in the step-and-shoot mode. One hundred and twenty images were acquired using a 128 x 128 matrix, in 3° steps at 15s per step. Raw images were inspected to ensure that no patient movement had occurred during the acquisition, in which case images were repeated. The radius of rotation and height of the imaging table were noted for each patient and used for the post-treatment study.

3.3.2.3 Image reconstruction

Data were reconstructed by filtered backprojection, using a Metz filter (power=5, FWHM=14mm). The Chang method (μ = 0.11/cm) was used for attenuation correction [Chang 1978]. The final reconstructed voxel size was 1.7x1.7x3.9 mm^3. Image files were converted from interfile to analyze format using conversion software (Medcon, Erik Nolf, UZ Ghent, Belgium).

3.3.3 Treatment Study

After baseline clinical assessments, which included MRI and SPECT imaging, patients with alcohol-induced psychotic disorder (n=20) were started on a daily dose of 5mg haloperidol (orally) and were maintained on this dose throughout the study. Extrapyrimidal side–effects, which were reported infrequently, were treated with benzhexol 2-6 mg/day and lorazepam 2-4mg/day was used if required for sedation or anxiety. Patients were clinically re-assessed after 3 weeks and at completion of the study (6 weeks). This included a follow-up SPECT study.

3.4 Statistical Analysis

3.4.1 Statistical Analysis: Psychopathology study component

Comparisons of the four groups with respect to continuous variables like PANSS and other rating scales etc. were done by using analysis of variance (ANOVA) techniques. Depending on the nature of the observations, standard methods based on normal distribution theory were used where possible. Certain distribution-free techniques, like those based on rankings were implemented otherwise. Where repeated measures were observed on each patient, the means were compared with either a paired t-test or if the data were not normally distributed, a Wilcoxin matched pairs test.

When nominal variables were compared, it was done by utilizing contingency tables. The maximum likelihood test rather than the Pearson chi-square test were used. Reliability analysis/internal consistency for each of the PANSS (positive, negative and general) scales were determined by calculating Cronbach's alpha coeficients. Statistical analyses in this component of the study were performed with a significance level of 5% ($p<0.05$).

3.4.2 Statistical Analysis: SPECT study components

Statistical analyses were conducted on a voxel-by-voxel basis using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, UK) [Friston et al. 1991]. The images of each subject were normalised to the Montreal Neurological Institute (MNI) standard anatomical space with 4x4x4 mm^3 voxels, and to a value of 50 using proportional scaling. This was

achieved using 12 affine transformations and 7x8x7 non-linear basis functions. The normalised images were then smoothed using a 3D Gaussian kernel with a FWHM of 12mm.

Analysis

Four study designs were employed. Firstly an unpaired t-test was used to compare rCBF between different subject groups. Secondly a paired t-test was used to detect changes in rCBF in alcohol induced psychosis patients following pharmacotherapy. Thirdly in the alcohol induced psychosis patients correlations were sought between baseline rCBF and PANNS scores, and finally correlations were sought between changes in rCBF and changes in PANNS scores in the same group.

To adjust for multiple comparisons an uncorrected p-value of $p<0.001$ was chosen as a threshold for statistical significance. A spatial extent threshold of 10 voxels was also used at all times. The first two analyses are also reported for an uncorrected p-value of $p<0.01$ in a number of regions determined a-priori to be likely to be involved in the pathophysiology of alcohol induced psychosis (frontal cortex, temporal cortex, basal ganglia, and thalami). Clusters were located to anatomical regions using MRIcro software (Chris Rorden, Nottingham University, UK).

4. RESULTS and DISCUSSION

Note: In order to preserve clarity and continuity, the discussion of each component of the study will follow immediately after the results.

4.1 Psychopathology Study Results

4.1.1 Demographics (See Tables 1 & 2)

The mean age, gender ratio and ethnic distribution were similar in all groups. The gender ratio and ethnic distribution reflects the demographics of the clinical population of patients with alcohol-induced psychotic disorder that was referred from our catchment area over the course of the study. Patients from the other groups were matched with the alcohol-induced psychotic disorder patient cohort based on age, gender and ethnicity. The alcohol-induced psychotic disorder group differed significantly with each of the other groups on the grade of education achieved ($p<0.01$) whilst no significant ($p>0.05$) differences were noted amongst the other 3 groups.

According to the histories obtained, patients with alcohol-induced psychotic disorder presented with the first onset of psychosis at a much later age than patients with schizophrenia (mean age: 36.22 vs.24.79 yrs; $p<0.01$). No statistical difference was found with regard to the age of onset of alcohol related symtoms amongst the two groups of patients with alcohol related symptomatology (mean age: 21.39 vs. 20.25 yrs; $p=0.46$). Although strong evidence of suicidal behaviour (attempts) was reported by the three patient groups, no statistical significant differences could be demonstrated.

Table 1: Demographic characteristics of the four study groups.

	Alcohol-Induced Psychotic Disorder (n=28)	Schizophrenia (n=21)	Alcohol Dependence (n=20)	Healthy Volunteers (n=19)	p values
Age (Mean/Range)	38.09 (23-51)	35.24 (19-55)	37.60 (24-54)	38.14 (23-56)	p=0.565 (AN)
Gender	M23/F5	M15/F6	M17/F3	M14/F5	p=0.659 (CHI)
Educational level (grade)	7.71	10.85	10.55	11. 89	p<0.0001 (KW)
Ethnicity	B26/W2/A0	B14/W6/A1	B16/W3/A1	B16/W3/A0	p=0.257 (CHI)

(Key to abbreviations: p values: AN=ANOVA; CHI=Likelihood ratio chi-square; KW= Kruskal-Wallis; MW=Mann-Whitney. Ethnicity: B=Brown; W=White; A=Black African)

Table 2: Histories of age of onset of illness and suicidal behaviour

	Alcohol-Induced Psychotic Disorder (n=28)	Schizophrenia (n=21)	Alcohol Dependence (n=20)	Healthy Volunteers (n=19)	p values
Age at onset of first psychotic symptoms (yrs)	36.22(23-50)	24.79(19-36)	N/A	N/A	p<0.01 (AN)
Age at onset of alcohol related symptoms (yrs)	21.39(12-39)	N/A	20.25(14-38)	N/A	p=0.46 (MW)
History of suicidal behaviour	n=10/28 (35.7%)	n=4/21 (19.0%)	n=6/20 (30%)	N/A	p=0.42 (CHI)

(Key to abbreviations: p values: AN=ANOVA; CHI=Likelihood ratio chi-square; KW= Kruskal- Wallis; MW=Mann-Whitney.)

4.1.2 Psychopathology - general (see Table 3)

Patients with clinically significant comorbid Axis I diagnoses such as major depressive disorder and anxiety disorders were excluded from this study. Nevertheless, patients with alcohol-induced psychotic disorder scored higher on anxiety and depressive symptoms compared to patients with schizophrenia, alcohol dependence and healthy volunteers. For the anxiety ratings on the Ham-A this reached statistical significance ($p<0.01$) compared to the schizophrenia group and healthy volunteers. With regard to depressive symptoms, patients with alcohol-induced psychotic disorder scored significantly higher on the Ham-D in comparison to patients with alcohol dependence and healthy volunteers, but not when compared with the schizophrenia group. However when depressive symptoms were assessed by the CDSS, statistical significance was achieved when compared to the schizophrenia group, but not with the alcohol-dependent group.

Mild cognitive impairment in the alcohol-induced psychotic disorder group was suggested by their mean score (27.96) on the MMSE which differed significantly from the alcohol dependent group (29.55; $p<0.01$) and healthy volunteers (29.79; $p<0.01$), but not from the schizophrenia group (28.76; $p=0.52$).

When comparing the severity of drinking in the two alcohol-related groups, it was interesting to note that the alcohol-dependent group scored significantly higher on the SADQ (38.45 vs. 25.92; $p<0.01$) compared to the alcohol-induced psychotic disorder group. There was however no significant

difference in the onset of general alcohol related symtoms between the two alcohol related patient groups.

A number of different measurement parameters suggested that patients with schizophrenia presented with more severe and disabling impairment than those with alcohol-induced psychotic disorder. Not only does the psychotic syndrome differ in severity on the CGI-SP (4.62 in schizophrenia group vs. 3.68 in alcohol-induced psychotic disorder group;$p<0.01$), but impairment of functioning as measured on SOF, is likewise more pronounced in the schizophrenia group (38.23 vs. 46.80; $p<0.01$) than in the group with alcohol-induced psychotic disorder. As may have been expected both psychotic disorder patient groups differed significantly from the alcohol dependant group in terms of agitated behaviour as measured on the ABS. Furthermore, the scores (18.86 in alcohol-induced psychotic disorder group vs. 31.95 in schizophrenia group; $p<0.01$) on the SUMD support the impression that patients with alcohol-induced psychotic disorder have a greater awareness of their illness as compared to patients with schizophrenia.

Table 3: Psychopathology - general

Mean Scores ±SD

Rating Scale	Alcohol-Induced Psychotic Disorder (n=28)	Schizophrenia (n=21)	Alcohol Dependence (n=20)	Healthy Volunteers (n=19)	p values/ Bonferroni comparisons
Hamilton Anxiety Scale	11.14±7.20	5.67±3.41	8.30±4.50	1.89±1.80	a,d,e,h,j,k
Hamilton Depression Scale	12.46±6.88	9.67±2.71	7.70±3.87	1.10±1.33	b,c,e,h,i,k
Calgary Depression Scale	4.64±4.14	1.76±1.84	3.80±1.88	0.26±0.56	a,d,e,h,j,k
Mini Mental State Examination	27.96±2.44	28.76±1.30	29.55±0.83	29.79±0.54	b,c,e,h,j,l
Agitated Behavior Scale (Corrigan)	18.46±2.55	20.1±3.11	15.45±1.47	N/A	b,c,g
Scale of Functioning	46.80±5.71	38.23±6.17	54.11±3.86	58.78±0.85	a,c,e,g,i,l
Severity of Alcohol Dependence Questionnairre	25.92±12.33	N/A	38.45±12.62	N/A	p<0.01 (AN)
Scale to assess unawareness of mental disorder	18.86±6.71	31.95±9.17	N/A	N/A	p<0.01 (MW)
Clinical Global Impression of Severity of Psychosis	3.68±0.90	4.62±0.97	N/A	N/A	P<0.01 (MW)

Key to p values (Bonferroni):
Alcohol-induced psychotic disorder vs. Schizophrenia: (a) p<0.01, (b) p>0.05;
Alcohol-induced psychotic disorder vs. Alcohol dependence: (c) p<0.01, (d) p>0.05);
Alcohol-induced psychotic disorder vs. Healthy volunteers: (e) p<0.01, (f) p>0.05;
Schizophrenia vs Alcohol dependence: (g) p<0.01, (h) p>0.05 ;
Schizophrenia vs Heathy volunteers: (i) p<0.01, (j) p>0.05 ;
Alcohol dependence vs Healthy volunteers: (k) p<0.01, (l) p>0.05.
Key to abbreviations: p values: AN=ANOVA; MW=Mann-Whitney.

4.1.3 Psychopathology: Psychotic features in alcohol-induced psychotic disorder compared to those in schizophrenia (Table 4)

Only the patients from the alcohol-induced psychotic disorder and schizophrenia groups (i.e. patients with psychotic disorders) were included in this comparison on the PANSS rating scale.

Patients with alcohol-induced psychotic disorder scored highly significantly ($p<0.01$) lower than those with schizophrenia on all three subscales as well as on total scores (19.89 vs. 24.38, on the positive subscale; 14.86 vs. 24.48, on the negative subscale; 35.68 vs. 42.67, on the general psychpatology subscale and 70.43 vs. 91.52 on the total scores).

Positive symptom subscale:

Internal consistency/reliability on the positive subscale was relatively low in the alcohol-induced psychotic disorder group (Cronbach's alpha = .41). This increased to .51 when the p3 Item (hallucinations) was deleted. This item was the only item on the positive subscale that was inversely correlated with the other positive subscale items in the alcohol-induced psychotic disorder group. Despite this, item p3 was included for further analysis, hallucinations being a core feature of both disorders.

Three individual items of the positive subscale namely pos2 (conceptual disorganization) and pos5 (grandiosity) scored highly significantly ($p<0.01$) and pos1 (delusions) significantly ($p<0.05$) lower in the alcohol-induced psychotic disorder group compared to the schizophrenia group. Only one item

namely pos3 (hallucinations) scored significantly ($p<0.05$) higher in the alcohol-induced psychotic disorder group compared to the schizophrenia group. No statistical differences between the two groups were found on the following items: pos4 (excitement), pos 6 (suspiciousness) and pos7 (hostility).

Negative symptom subscale:

Internal consistency/reliability on the negative subscale was relatively high in the combined population (Cronbach's alpha = .90).

Except for item neg5 (difficulty in abstract thinking), all items on the negative subscale rated highly significantly ($p<0.01$), [items neg1 (blunted affect), neg2 (emotional withdrawal), neg3 (poor rapport), neg4 (passive/apathetic social withdrawal) and neg7 (stereotyped thinking)], or significantly ($p<0.05$), [item neg6 (lack of spontaneity and flow of conversation)], lower in the alcohol-induced psychotic disorder group compared to the schizophrenia group. Overall, all mean scores for items on the negative subscale were lower in the alcohol-induced psychotic disorder group.

No statistically significant difference between the groups was found on the following item: neg5 (difficulty in abstract thinking).

General psychopathology subscale:

Internal consistency/reliability on the negative subscale in the combined population was acceptable (Cronbach's alpha =0.62).

Mean scores of seven of the 16 items on the general psychopathology scale were either highly significantly ($p<0.01$), [items gen7 (motor retardation), gen9 (unusual thought content), gen12 (lack of judgement and insight), gen13 (disturbance of volition), gen15 (pre-occupation) and gen16 (active social avoidance], or significantlly ($p<0.05$) [item gen5 (mannerisms and posturing)], lower in the alcohol-induced psychotic disorder group when compared to the schizophrenia group. Three items, [gen2 (anxiety), gen4 (tension), and gen6 (depression)] scored significantly ($p<0.05$) higher in the alcohol-induced psychotic disorder group.

No statistical differences between the two groups were found in the mean scores of the following items: gen1 (somatic concern), gen3 (guilt feelings), gen8 (uncooperativeness), gen 10 (disorientation), gen11 (poor attention) and gen14 (poor impulse control).

Table 4 : Psychopathology - psychotic features

PANSS positive scale	Alcohol- Induced Psychotic Disorder (n=28) Mean ± SD	Schizophrenia (n=21) Mean ± SD	p values (MW)
Pos1	3.93 ± 1.18	4.62 ± 1.02	p = 0.04 *
Pos2	1.18 ± 0.39	4.14 ± 1.35	p < 0.01 **
Pos3	4.07 ± 1.02	3.29 ± 1.27	p = 0.02 *
Pos4	2.82 ± 1.12	3.10 ± 1.14	p =0.38
Pos5	1.36 ± 0.73	2.76 ± 1.51	p< 0.01 **
Pos6	4.11 ± 1.42	3.90 ± 1.45	p = 0.59
Pos7	2.46 ± 0.92	2.52 ± 1.17	p = 0.87
Positive Total	19.89 ± 3.31	24.38 ± 4.61	P< 0.01 **
PANSS negative scale	Alcohol- Induced Psychotic Disorder (n=28) Mean ± SD	Schizophrenia (n=21) Mean ± SD	p values
Neg1	1.61± 1.03	3.29 ± 1.06	p<0.01**
Neg2	2.25 ± 1.04	3.90 ± 0.83	p<0.01**
Neg3	1.61 ± 1.34	2.90 ± 1.26	p<0.01**
Neg4	2.29 ± 1.15	4.19 ± 0.81	p<0.01**
Neg5	3.21 ± 1.50	3.95 ± 1.66	p=0.13
Neg6	2.04 ± 1.29	2.90 ± 1.45	p=0.03 *
Neg7	1.86 ± 1.01	3.33 ± 1.11	p<0.01 **
Negative Total	14.86 ± 6.33	24.48 ± 6.01	P<0.01 **
PANSS general scale	Alcohol- Induced Psychotic Disorder (n=28) Mean ± SD	Schizophrenia (n=21) Mean ± SD	p values
Gen1	1.68 ± 1.16	2.48 ± 1.81	p=0.13
Gen2	3.32 ± 0.86	2.62 ± 0.97	p=0.02 *
Gen3	1.71 ± 0.98	1.48 ± 0.81	p=0.47
Gen4	2.68 ± 0.77	2.10 ± 0.77	p=0.02 *
Gen5	1.04 ± 0.19	1.57 ± 0.87	p=0.04 *
Gen6	2.93 ± 1.46	1.95 ± 0.92	p=0.02 *
Gen7	2.04 ± 1.29	3.24 ± 1.22	p<0.01**
Gen8	1.54 ± 0.74	1.81 ± 0.87	p=0.28
Gen9	2.96 ± 1.04	3.81 ± 0.93	p<0.01 **
Gen10	1.32 ± 0.72	1.52 ± 0.87	p=0.52
Gen11	1.64 ± 0.91	2.05 ± 1.24	p=0.35
Gen12	3.57 ± 0.88	4.67 ± 0.86	p<0.01 **
Gen13	2.18 ± 1.02	3.76 ± 0.94	p<0.01 **
Gen14	2.61± 1.10	2.71 ± 0.85	p=0.66
Gen15	1.79 ± 0.96	3.19 ± 1.33	p<0.01 **
Gen16	2.71 ± 1.12	3.71 ± 0.85	p<0.01 **
General Total	35.68 ± 7.19	42.67 ± 5.79	p<0.01 **
Total Score	70.43 ± 13.39	91.52 ± 12.65	p<0.01 **

(*Significant p<0.05; and ** highly significant p<0.01)

Symptom definitions: **Positive subscale**: pos1, delusions; pos2, conceptual disorganization; pos3, hallucinations; pos4, excitement; pos5, grandiosity; pos6, suspiciousness/persecution; pos7, hostility. **Negative subscale**: neg1, blunted affect; neg2, emotional withdrawal; neg3, poor rapport; neg4, passive/apathetic social withdrawal; neg5, difficulty in abstract thinking; neg6, lack of spontaneity and flow of conversation; neg7, stereotyped thinking. **General Subscale**: gen1, somatic concern; gen2, anxiety; gen3, guilt feelings; gen4, tension; gen5, mannerisms and posturing; gen6, depression, gen7, motor retardation; gen8,uncooperativeness; gen9, unusual thought content; gen10, disorientaion; gen11, poor attention; gen12, lack of judgement and insight; gen13, disturbance of volition; gen14, poor impulse control; gen15, preoccupation; gen16, active social avoidance.

Severity of symptoms on all subcales: (Table 5)

All items on the PANSS rating scale are rated as follows: 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe and 7=extreme. Based on PANSS mean scores ratings ≥ 3, the following psychotic syndrome profiles emerged for each group: (see table 5).

Patients with alcohol-induced psychotic disorder predominantly presented with delusions, hallucinations, suspiciousness, difficulty in abstract thinking, anxiety and lack of judgement and insight. It is of particular interest that low mean scores (<2) on conceptual disorganization, grandiosity, blunted affect, poor rapport, stereotyped thinking, somatic concern, guilt feelings, mannerisms and posturing, uncooperativeness, disorientation, poor attention and pre-occupation, were noted in the alcohol-induced psychotic disorder group. This suggests the virtual absence of these symptoms in this group.

On the other hand, presenting symptoms (mean scores ≥ 3) in the schizophrenia group also included conceptual disorganization, excitement and negative symptoms such as blunted affect, emotional withdrawal, passive/apathetic social withdrawal and stereotyped thinking. On the general

scale, motor retardation, unusual thought content, disturbance of volition, pre-occupation and active social avoidance completed the expected schizophrenic syndrome. The general scale item with mean score ≥ 3 in the alcohol-induced psychotic disorder group not equaled in the schizophrenia group was anxiety.

Table 5: Severity of symptoms (PANSS mean scores ≥3)

PANSS item positive scale	**Alcohol-Induced Psychotic Disorder (n=28) Mean score**	**PANSS item positive scale**	**Schizophrenia (n=21) Mean score**
P1 (delusions)	3.93	P1 (delusions)	4.62
		p2(conceptual disorganization)	4.14
p3 (hallucinations)	4.07	p3 (hallucinations)	3.29
		p4 (excitement)	3.10
p6 (suspiciousness)	4.11	p6 (suspiciousness)	3.90
PANSS item Negative scale		**PANSS item Negative scale**	
		N1 (blunted affect)	3.29
		n2 (emotional withdrawal)	3.90
			4.19
		n4 (passive/appathetic social withdrawal)	3.95
n5 (difficulty in abstract thinking)	3.21	n5 (difficulty in abstract thinking)	3.33
		n7(stereotyped thinking)	
PANSS item general scale		**PANSS item general scale**	
G2 (anxiety)	3.32	G7(motor retardation)	3.24
		g9 (unusual thought content)	3.81
g12 (lack of judgement and insight)	3.57	g12 (lack of judgement and insight)	4.67
		g13 (disturbance of volition)	3.76
		g15 (pre-occupation)	3.19
		g16 (active social avoidance)	3.71

Five-factor analysis of the PANSS: (Table 6)

Although originally designed with 3 subscales, several factor analytical studies of the PANSS have preferentially yielded 5 factors, namely negative, positive (psychotic), disorganized, excited and depression and anxiety factors (Emsley et al, 2003). We also compared alcohol-induced psychotic disorder to schizophrenia on the five-factor structure for schizophrenia. Less specific items (n7, g1, g4, g5, g13 and g15) were excluded as these factors are believed not to significantly effect the PANSS factor structure (Emsley et al, 2003). Two factor components namely the negative factor component and the disorganized factor component scored highly significantly (p>0.01) lower in the alcohol-induced psychotic disorder group. The scores on the excitement component did not differ significantly between the groups. With regard to the remaining factor components, the alcohol-induced psychotic disorder group scored significantly higher and lower than the schizophrenia group with regard to the depression/anxiety factor and psychosis factor components respectively.

Table 6: Five-factor analysis of the PANSS

	Cronbach – alpha	Alcohol-Induced Psychotic Disorder (n=28) **Mean score**	Schizophrenia (n=21) **Mean score**	**p values (MW)**
Psychosis factor (p1,p3, p5, p6, g9,g12)	.53	3.33	3.84	P<0.05 *
Negative factor (n1,n2,n3,n4,n6,g7,g16)	.93	2.08	3.45	p<0.01 **
Disorganized factor (p2,n5,g10,g11)	.60	1.84	2.92	p<0.01 **
Excitement factor (p4,p7,g8,g14)	.74	2.36	2.54	P=0.41
Depression/Anxiety factor (g2,g3,g6)	.70	2.65	2.02	P<0.05 *

4.1.4 Psychopathology in Alcohol-Induced Psychotic Disorder: PANSS ratings before and after anti-psychotic treatment (Table 7)

Wilcoxin's matched pairs test (WILC) were used in all the analyses in Table 7 since the repeated measurements were mostly not normally distributed. Highly statistically significant clinical improvements were noted on the positive ($p<0.0001$) and general psychopathology ($p<0.001$) subscales, as well as on the total score ($p<0.001$), of the PANSS. No significant improvement ($p<0.07$) was measured on the negative symptom subscale of the PANSS.

Positive symptom subscale

Highly statistically significant improvements ($p<0.01$) were noted on five of the individual items of the positive symptom subscale. No significant improvement was evident on the pos2 (conceptual disorganization) and pos 5 (grandiosity) items. Both of these items however scored extremely low (<2) at baseline suggesting no clinically significant psychopathology on these measures in patients with alcohol-induced psychotic disorder.

Negative symptom subscale

Statistically significant improvements ($p<0.05$) were evident on three of the individual items of the negative subscale, namely neg2 (emotional withdrawal), neg4 (passive/apathetic social withdrawal) and neg7 (stereotyped thinking). Low mean baseline scores (<3) on these three items however suggest only a mild degree of clinical severity. Interestingly, no significant improvement was noted on the neg5 (difficulty in abstract thinking) item that showed the highest mean negative item score at baseline.

General psychopathology subscale

Items that showed highly statistically significant improvements ($p<0.01$) on the general psychopathology subscale of the PANSS were the following: gen2 (anxiety), gen4 (tension), gen6 (depression), gen9 (unusual thought content), gen 12 (lack of judgement and insight), gen14 (poor impulse control) and gen16 (active social avoidance). Items gen11 (poor attention) and gen 15 (pre-occupation) showed statistically significant improvement ($p<0.05$) after the six weeks of anti-psychotic treatment.

Table 7: Psychopathology in Alcohol-Induced Psychotic Disorder before and after anti-psychotic treatment

PANSS positive scale	**Mean score before treatment n=20**	**Mean score after treatment n=20**	**p values (WILC)**
Pos1	4.0	1.65	p<0.0001 **
Pos2	1.15	1.00	p=0.11
Pos3	3.95	1.35	p<0.001 **
Pos4	2.95	1.25	p<0.001 **
Pos5	1.30	1.10	p=0.18
Pos6	4.20	1.15	p<0.001 **
Pos7	2.35	1.25	p<0.01 **
Positive Total	19.85	9.10	p<0.0001
PANSS negative scale	**Mean score before treatment n=20**	**Mean score after treatment n=20**	**p values (WILC)**
Neg1	1.35	1.30	p=0.83
Neg2	2.05	1.45	p<0.05 *
Neg3	1.40	1.25	p=0.55
Neg4	2.25	1.45	p<0.05 *
Neg5	3.20	2.65	p=0.06
Neg6	1.65	1.55	p=0.79
Neg7	1.65	1.20	p<0.05 *
Negative Total	13.55	11.30	p=0.07
PANSS General scale	**Mean score before treatment n=20**	**Mean score after treatment n=20**	p values (WILC)
Gen1	1.65	1.30	p=0.36
Gen2	3.25	1.70	p<0.001 **
Gen3	1.50	1.15	p=0.06
Gen4	1.73	1.45	p<0.01 **
Gen5	1.05	1.00	p=0.06
Gen6	2.65	1.55	p<0.01 **

Gen7	1.70	1.60	p=0.79
Gen8	1.30	1.05	p=0.09
Gen9	3.00	1.25	p<0.001 **
Gen10	1.30	1.00	p=0.11
Gen11	1.50	1.00	p<0.05 *
Gen12	3.55	1.50	p<0.001 **
Gen13	1.95	1.65	p=0.25
Gen14	2.40	1.15	p<0.01 **
Gen15	1.75	1.05	p<0.05 *
Gen16	2.55	1.50	p<0.01 **
General Total	33.70	20.90	p<0.001 **
Total Score	67.10	40.85	p<0.001 **

Symptom definitions: **Positive subscale**: pos1, delusions; pos2, conceptual disorganization; pos3, hallucinations; pos4, excitement; pos5, grandiosity; pos6, suspiciousness/persecution; pos7, hostility. **Negative subscale**: neg1, blunted affect; neg2, emotional withdrawal; neg3, poor rapport; neg4, passive/apathetic social withdrawal; neg5, difficulty in abstract thinking; neg6, lack of spontaneity and flow of conversation; neg7, stereotyped thinking. **General Subscale**: gen1, somatic concern; gen2, anxiety; gen3, guilt feelings; gen4, tension; gen5, mannerisms and posturing; gen6, depression, gen7, motor retardation; gen8,uncooperativeness; gen9, unusual thought content; gen10, disorientaion; gen11, poor attention; gen12, lack of judgement and insight; gen13, disturbance of volition; gen14, poor impulse control; gen15, preoccupation; gen16, active social avoidance.

4.2 Discussion of Psychopathology Study

This study not only supported the existence of alcohol-induced psychotic disorder as a discrete clinical entity, but also shed more light on demographic and psychopathological factors that have hitherto not been systematically assessed.

Patients with alcohol-induced psychotic disorder first developed psychosis at an older age compared to patients with schizophrenia (Johansson, 1961; Glass, 1989). This was confirmed by our study where the mean **age of onset of psychosis** was 36.22 years in the alcohol-induced psychosis group and 24.79 years in the schizophrenia group. This corresponds to the older mean age of onset of 37.4 years for alcohol-induced psychosis and 32.8 years for (paranoid) schizophrenia reported by Soyka (1990).

An interesting finding in our study was the distinct **lower educational level** found in the alcohol-induced psychotic disorder group when compared to alcohol dependent and schizophrenia patient groups. This does not seem to correspond to other variables that suggest better insight & judgement (on PANSS gen12 and SUMD), lesser degree of psychosis (CGI-SP) and higher level of functioning (SOF) in the alcohol-induced psychotic disorder group compared to the schizophrenia group. Whether a lower educational level reflects a developmental deficit or vulnerability, or an external risk factor (other than alcohol) is uncertain.

A greater degree of alcohol use, as suggested by Tsuang (1994), could have partially explained an increased vulnerability to the development of alcohol-induced psychotic disorder, especially when occurring at a later age. Life-time alcohol use could have been greater in the in the alcohol-induced-psychotic disorder group, but was not specifically assessed. It must be noted though that the mean age (38.09 vs. 37.60yrs) and mean age of onset of alcohol related symtoms (21.39 vs. 20.25yrs) were neither statistically significantly different in the alcohol-induced psychotic disorder and alcohol-dependence groups respectively. Accumulative exposure to the toxic effects of alcohol may however contribute to psychosis. However, our findings do not support a greater degree of alcohol dependence in the alcohol-induced psychotic disorder group as measured on the Severity of Alcohol Dependence Questionairre (SADQ). Given that this is a subjective rating instrument relying on the patient's personal account of severity, further objective study including assessment of lifetime alcohol use is warranted.

Tsuang (1994) also considered the possibility that concomitant **abuse of other substances** in patients with primary alcohol dependence may be a risk factor for the development of alcohol-induced psychotic disorder. Once again, our findings do not support this. We excluded all recent (< 6 months) and current substance abuse in all patient groups on the basis of personal and collateral histories as well as random toxicology screening prior to entering the study. Comorbid substance abuse was thus highly unlikely to contribute directly to the development of psychotic symptoms in our patient cohort.

The MMSE was primarily used as an instrument to exclude patients with clinically significant comorbid cognitive impairment in this study. Whilst it is acknowledged that it is not a sophisticated instrument for the assessment of cognitive impairment, our findings do indicate a mild degree of **cognitive impairment** in the alcohol-induced psychotic disorder patient group compared to healthy volunteers and to patients with alcohol dependence, but not when compared to patients with schizophrenia. Whether factors such as substance abuse during early childhood or adolescence, possibly associated with a low level of education and mild cognitive deficit, predispose to the development of psychotic symptoms in later life is a theoretical possibility worth further exploration. Of further interest may be to consider the protective factors allowing the delay of onset of psychotic symptoms until the third or fourth decades.

Soyka (1988) reported a **history of suicidal behaviour** in 17.6% of patients with alcoholic hallucinosis. This corresponds to the 35.7% of patients with

alcohol-induced psychotic disorder in our study that reported previous suicidal behaviour. Whilst the groups did not differ statistically, suicidality remains a clinical significant entity in the clinical presentation and management of patients with alcohol-induced psychotic disorder.

Comorbid **anxiety and depressive symptoms** in alcohol-induced psychotic disorder have also been reported previously (Soyka 1990). In this study these symptoms occurred significantly more in the alcohol-induced psychotic disorder group compared to the schizophrenia group. The exclusion criteria disallowed patients with comorbid anxiety or depressive disorders, but no patients were excluded from this study on these grounds. Depressive and anxiety symptoms as measured on the PANSS improved along with psychotic features without anti-depressant intervention. These symptoms therefore seem to occur as symptoms of alcohol-induced psychotic disorder or alcohol abuse rather than representing independent anxiety or depressive disorders.

A number of important aspects with regard to the psychotic features of alcohol-induced psychotic disorder emerged from this study. Firstly, it clear that patients with alcohol-induced psychotic disorder generally presented with **significantly less severe psychotic features, better jugdement, insight and awareness of their condition and less functional impairment** than patients with schizophrenia. Alcohol-induced psychotic disorder appears to be devoid of specific schizophrenic symptoms such as **thought process disorder** as suggested by the extremely low and highly significant difference from schizophrenia on the mean score on item pos2 **(conceptual**

disorganization). This is also supported by a highly significant difference on the disorganized factor component in the five-factor analysis. Of special interest is the lower levels of **negative symptoms,** usually associated with schizophrenia, found in the patients alcohol-induced psychotic disorder. This is supported by the highly significant difference between the groups on the negative subscale of the PANSS, negative factor component of the five-factor analysis and individual items such as blunted affect (neg1). Symptoms suggestive of bipolar disorder (mania) such as grandiosity were also extremely remote.

Interestingly, patients showed significant improvement with treatment on the positive, general and total scores but not on the negative scale of the PANSS. Symptoms associated with the psychotic syndrome (eg. hallucinations and delusions) and general symptoms (eg. anxiety and depressive features) as reflected by the positive and general subscales of the PANSS respectively, appear to be relatively reversible and possibly more representative of alcohol-induced psychotic disorder itself.

Identifying symptoms and signs that can be considered as typical of the alcohol-induced psychotic syndrome is not only of clinical importance, but has valuable research potential. One set of symptoms and signs of alcohol-induced psychotic disorder that may be of special interest when exploring the biological underpinnings of alcohol-induced psychotic disorder would be those that differ significantly from schizophrenia. Secondly, it would be of similar importance to explore those symptoms and signs of alcohol-induced psychotic

disorder that show a consistent degree of severity and also respond to treatment. These aspects comprised the second and third components of our study and will be discussed in the next sections.

4.3 SPECT Study Results.

4.3.1 Demographics

The demographic composition of the sample for this part of the study was similar to that of the psychopathology study. The alcohol-induced psychotic disorder group consisted of 19 participants (15 male, 4 female) with a mean (SD) age of 39 (4) years; the schizophrenia group consisted of 16 participants, (11 male, 5 female) with a mean (SD) age of 35 (10) years; the alcohol dependent group consisted of 20 participants (17 male, 3 female) with a mean (SD) age of 38 (7) years and the healthy volunteer group consisted of 19 participants (14 male, 5 female) with a mean (SD) age of 37 (8) years. All the participants included in this part of the study also participated in the psychopathology component of the study. The main reason for non-inclusion of patients from the original group in this part of the study was lack of informed consent.

4.3.2 SPECT rCBF Results

Note: Not all the results are reported for the same level of statistical significance in this component of the study. Given the large number of independant variables arising from SPECT studies and the fact that a result with a level of significance of $p<0.01$ has a 1% rate of occurrence by chance, it is to be expected that some results will reflect type I errors. However in the

case of results with a level of significance of $p \leq 0.001$, these errors are expected to be far less common.

4.3.2.1 Regional Cerebral Blood Flow (rCBF) in patients with Alcohol-Induced Psychotic Disorder vs Healthy Volunteers (comparing Frontal lobes, Temporal lobes, Basal ganglia and Thalamus) .

The rCBF showed higher flow in all four anatomical regions investigated in patients with alcohol-induced psychotic disorder compared with healthy volunteers. Increased bilateral frontal and temporal lobe perfusion was noted as well as increased flow in the regions of the left thalamus and the right basal ganglia (Table 8). No areas of reduced flow in these areas were noted in patients with alcohol-induced psychotic disorder.

Table 8: rCBF higher in patients with Alcohol-induced Psychotic Disorder compared to Healthy Volunteers.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
48	**3.69**	**p<0.001**	**16,52,8**	**Frontal Sup Medial R**
21	**3.42**	**p<0.001**	**-44,0,24**	**Frontal deep to Pre-central L**
51	3.33	p<0.01	16,-4,0	Pallidum R
105	3.23	p<0.01	36,8,-28	Temporal pole Mid R
34	3.17	P<0.01	-48,-48,0	Temporal Mid L
37	2.97	P<0.01	-16,-12,-4	Thalamus L
17	2.95	P<0.01	-24,48,8	Frontal Mid L
16	2.8	P<0.01	48,-56,0	Temporal Mid R
9	2.78	P<0.01	-44, 4, -28	Temporal Inf L
5	2.58	P<0.01	-16,36,36	Frontal Sup L

(Height thresholds: T=2.43, p=0.01 and for T=3.33, p=0.001)

4.3.2.2 Regional Cerebral Blood Flow (rCBF) in patients with Alcohol-Induced Psychotic Disorder vs patients with Schizophrenia (comparing Frontal lobes, Temporal lobes, Basal ganglia and Thalamus).

These results were diverse and statistically significant differences were limited to the right mid-temporal region and the left inferior frontal lobe which showed higher and lower flow respectively in patients with alcohol-induced psychotic disorder in comparison to patients with schizophrenia. (Tables 9 & 10).

Table 9: rCBF higher in patients with Alcohol-induced Psychotic Disorder compared to patients with Schizophrenia

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
32	3.31	p<0.01	52,-64,24	Temporal Mid R

(Height thresholds: T=2.44, p=0.01 and for T=3.36, p=0.001)

Table 10: rCBF lower in patients with Alcohol-induced Psychotic Disorder compared to patients with Schizophrenia.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
10	**3.44**	**p<0.001**	**-32,12,28**	**Frontal Inf Tri L**

(Height thresholds: T=2.44, p=0.01 and for T=3.36, p=0.001)

4.3.2.3 Regional Cerebral Blood Flow (rCBF) in patients with Alcohol-induced Psychotic Disorder vs patients with Alcohol Dependence (comparing Frontal lobes, Temporal lobes, Basal ganglia and Thalamus).

These results suggest higher rCBF in the parahippocampal region of the left temporal lobe in patients with alcohol-induced psychotic disorder when compared with patients with alcohol dependence.

It also showed comparatively **reduced flow to** components of three of the four anatomical brain regions, mainly to **the left inferior and mid-frontal lobe, the left basal ganglia and to the mid-temporal lobes bilaterally**. (Tables 11 & 12).

Table 11: rCBF higher in patients with Alcohol-induced Psychotic Disorder compared to patients with Alcohol Dependence.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
8	2.73	p<0.01	-12,4,-20	Parahippocampal L

(Height thresholds: T=2.43, p=0.01 and for T=3.33, p=0.001)

Table 12: rCBF lower in patients with Alcohol-induced Psychotic Disorder compared to patients with Alcohol Dependence.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
103	**4.09**	**p<0.001**	**-40,40,-4**	**Frontal Inf Orb L**
44	**3.48**	**p<0.001**	**-20,16,-4**	**Putamen L**
17	3.29	p<0.01	-36,24,52	Frontal Mid L
47	3.26	p<0.01	56,-44,-4	Temporal Mid R
99	3.17	p<0.01	-56,-56,4	Temporal Mid L
44	3.15	p<0.01	16,40.44	Frontal Sup R
7	3.02	p<0.01	16,32,-20	Frontal Sup Orb R
10	2.84	p<0.01	-44,20,20	Frontal Inf Tri L
7	2.65	p<0.01	20,24,4	Caudate R

(Height thresholds: T=2.43, p=0.01 and for T=3.33, p=0.001)

4.3.2.4 Regional Cerebral Blood Flow (rCBF) post vs pre treatment in patients with Alcohol-induced Psychotic Disorder (comparing Frontal lobes, Temporal lobes, Basal ganglia and Thalamus) .

Anti-psychotic treatment did not appear to have a uniform effect on rCBF when comparing SPECT variables before and after a six week treatment period in patients with alcohol-induced psychotic disorder. **Areas of both de-activation and activation** were noted. Post-treatment de-activation was detected mainly in the left frontal lobe and in the right temporal lobe (Table 13). Post–treatment activation was also mainly evident in the left frontal lobe (different clusters) and the left basal ganglia. (Table 14)

Table 13: De-activation of rCBF post vs pre therapy in patients with Alcohol-induced Psychotic Disorder.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
12	3.19	p<0.01	-20,32,32	Frontal Sup L
7	3.15	p<0.01	-20,52,-20	Frontal Mid Orb L
5	3.11	p<0.01	40,-4,-20	Hippocampus R
5	2.98	p<0.01	36,52,-12	Frontal Mid Orb R
6	2.96	p<0.01	40,-20,-8	Hippocampus R
5	2.76	p<0.01	-40,28,-16	Frontal Inf Orb L

(Height thresholds: T=2.55, p=0.01 and for T=3.61, p=0.001)

Table 14: Activation of rCBF post vs pre therapy in patients with Alcohol-induced Psychotic Disorder.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
54	**4.07**	**p<0.001**	**-8,0,68**	**Supplementary Motor Area L**
62	**3.89**	**p<0.001**	**-12,16,12**	**Caudate L**
38	**3.75**	**p<0.001**	**-48,-20,20**	**Rolandic Operculum L**
24	3.2	p<0.01	-24,-24,,64	Frontal Pre-central L
8	3.08	p<0.01	0,-12,40	Cingulum Mid

(Height threshold: T=2.55, p=0.01 and for T=3.61, p=0.001)

4.4 Discussion of SPECT Study

Following the aims set out for this study, the SPECT results supported baseline differences of regional cerebral blood flow (rCBF) between patients with alcohol-induced psychotic disorder and healthy volunteers, patients with schizophrenia and patients with alcohol dependence respectively. These differences were not demonstrated to the same level of significance and comparisons between the groups will be discussed separately.

Differences in regional cerebral perfusion in patients with alcohol-induced psychotic disorder were postulated to be demonstrable in the basal ganglia, thalamus, frontal and temporal lobes on the basis of case reports by Soyka et al (2000a, 2000b, 2005) and Kitabayashi et al (2007). Support for this was found in our study especially in the frontal and temporal lobes and basal ganglia with less convincing differences demonstrated in the thalamus. The resting cerebral perfusion differences in these brain regions will be discussed along with changes noted before and after 6 weeks of anti-psychotic therapy.

4.4.1 Regional cerebral blood flow in patients with alcohol-induced psychotic disorder vs healthy volunteers.

Unlike case reports suggesting reduced flow to various brain regions in alcohol-induced psychotic disorder (Soyka et al 2000a, 2000b, 2005 Kitabayashi et al 2007), this component of the current study points to the contrary. The brain regions investigated showed significantly **increased resting perfusion** in patients with alcohol-induced psychotic disorder compared to healthy volunteers, particularly to the **frontal and temporal**

lobes (bilaterally) and the regions of the right pallidum and left thalamus.

These findings are similar to reports on rCBF in alcohol withdrawal (Berglund & Risberg, 1981; Caspari et al, 1993) suggesting increased functional activity in portions of the temporal cortex in patients with alcohol withdrawal and lends some support to the hypothesis that alcohol-induced psychosis is a variant of alcohol withdrawal (Gross et al, 1968, 1970, 1972a, 1972b). Increased functional activity in the temporal lobes was also associated with auditory hallucinations in two patients with alcohol withdrawal (Berglund & Risberg, 1981). Alcohol withdrawal was however also associated with decreased functional activity in other regions especially during the first two days of withdrawal (Berglund & Risberg, 1981). Heterogeneous regional activity was thus suggested implying increased activity in some areas and decreased in others. Post-withdrawal assessments indicated relative elevation of cerebral blood flow in inferior temporal regions and reduction in the superior temporal regions during alcohol withdrawal (Caspari et al, 1993). Lyons et al (1998) postulated that diminished functional activity in alcohol withdrawal may be a function the length of chronic alcohol abuse, while increased activity noticed in the withdrawal state may be related to auditory hallucinations and agitation.

Note: Patients with concurrent alcohol-withdrawal were excluded from the study and some patients had relapsing psychotic features clearly associated with alcohol intoxication and/or withdrawal that did not clear upon abstinence prior to entering the study.

Notwithstanding the clinical differences between alcohol-induced psychotic disorder and alcohol withdrawal, the shared increased regional cerebral flow, particularly to the temporal lobes, demonstrated in this study, may be indicative of mutually shared impaired neuronal mechanisms underlying the pathogenesis of these two alcohol-related psychiatric disorders.

No significantly reduced cerebral flow compared to healthy volunteers could be demonstrated in any of the areas investigated. Reduced flow to the thalamus as suggested in case reports by Soyka (2000a, 2000b, 2005) and Kitabayashi (2007) could thus not be confirmed. However this is the first study of rCBF in groups of subjects. Given some evidence of increased flow to the left thalamus noted in our study, asymmetric rCBF to the thalamus remains a plausible explanation for some of their findings.

4.4.2 Regional cerebral blood flow in patients with alcohol-induced psychotic disorder vs schizophrenia.

Psychopathological differences between alcohol-induced psychotic disorder and schizophrenia may be reflected by baseline perfusion group differences. The significantly **higher rCBF found in one cluster of the right mid-temporal lobe** in patients with alcohol-induced psychotic disorder compared to those with schizophrenia is similar to the higher rCBF to the right mid–temporal lobe detected in our comparison of alcohol-induced psychotic disorder patients with healthy volunteers. Hypoperfusion to the temporal lobes in schizophrenia as indicated in previous reports (Crow 1990, Paulman

et al 1990, Catafau et al 1994, Klemm et al 1996) could also accentuate such a comparative finding.

The comparative **reduced flow in a small cluster of the the left frontal lobe** in the alcohol-induced psychotic disorder group is interesting. It could be postulated that it is consistent with decreased rCBF to the frontal lobes reported in alcohol dependence (Moselhy et al, 2001). These results lend some support to the view that different neuronal mechanisms are operative in alcohol-induced psychotic disorder and schizophrenia. Differences in thalamic and striatal rCBF between patients with alcohol-induced psychotic disorder and schizophrenia are amongst the possible abnormalities that could not be demonstrated. These findings however, do not exclude the possibility of a shared biological substrate in these disorders.

4.4.3 Regional cerebral blood flow in patients with alcohol-induced psychotic disorder vs alcohol dependence.

Although these results suggest some increased rCBF in the parahippocampal region of the left temporal lobe in patients with alcohol-induced psychotic disorder when compared to patients with alcohol dependence, the majority of the differences demonstrate areas with relatively lower flow in patients with alcohol-induced psychotic disorder .

Following the generally increased rCBF demonstrated in patients with alcohol-induced psychotic disorder, when compared to healthy volunteers, the expectation may have been to predict similar increased rCBF trends when

comparing rCBF in patients with alcohol dependence. Our findings however suggest predominantly **reduced relative rCBF to portions of the left frontal lobe, the left putamen, and the mid-temporal lobe bilaterally** in patients with alcohol-induced psychotic disorder. The role of these areas of reduced rCBF in patients with alcohol-induced psychotic disorder remains to be determined. The possibility is that it represents areas of more severe impairment in patients already known with alcoholism.

The only area that showed relatively **increased rCBF is the left parahippocampal gyrus**. These differences may reflect a possible role of this area in the pathogenesis of hallucinations in alcohol-induced psychotic disorder. The left parahipppocampal gyrus is one of the areas reported to be associated with hallucinations and increased brain activity in patients with schizophrenia (Silbersweig et al, 1995).

4.4.4 Regional cerebral blood flow in patients with alcohol-induced psychotic disorder pre- vs post-therapy.

Areas associated with significantly higher rCBF in patients with alcohol-induced psychotic disorder in comparison to healthy volunteers could be expected to show **post-therapy de-activation**. Two such areas were identified. Two clusters were in the **left superior frontal lobe** (MNI coordinates: -16,36,36 and -20,32,32) associated with increased rCBF vs volunteers and with decreased rCBF post vs pre-therapy. Two other clusters were in the **right mid temporal/ hippocampus region** (MNI coordinates: 36,8,-28, and 40,-4,-20) associated with increased rCBF vs volunteers and

with decreased rCBF post vs pre-treatment. Given the limited spatial resolution of SPECT, the coordinates of these two pairs of clusters are close enough (<20mm) to represent the same anatomical areas. **These findings could be interpreted as a post-treatment normalization of activation of rCBF in alcohol-induced psychotic disorder.** Alternatively, they may reflect a general improvement following abstinence from alcohol. This possibility however seems less likely, because previous reports suggest that post-abstinence is associated with increased rCBF, especially to the frontal lobes (Ishikawa et al, 1986; Lyons et al 1998; Gansler et al 2000 and Moselhy et al, 2001). In addition, these specific clusters did not show increased baseline rCBF when compared to the alcohol-dependent group. (Unfortunately however, these areas did not show any positive correlations between change in rCBF and improvement on any of the PANSS ratings in the treatment study. See next section.)

Further supportive evidence for **right mid-temporal** involvement comes from the fact that other right mid-temporal clusters also showed significant rCBF differences when compared to healthy volunteers and schizophrenia (increased flow) and alcohol dependence (reduced flow) groups.

The right mid-temporal region has been implicated in the pathogenesis of hallucinations in schizophrenia. Because the temporal cortex is regarded as a final destination for the perception of complex speech, it may include auditory hallucinations. A number of studies have reported an association between activation in the language areas and auditory hallucinations (Woodruff et al,

2004). These include the superior temporal gyri (bilateral) and the right mid-temporal region. Woodruff et al, 1997 (utilizing functional MR Imaging) reported that external speech activated the temporal cortex (especially the right middle temporal gyrus and the left superior temporal gyrus) less extensively in the in the presence than the absence of active auditory hallucinations in patients with schizophrenia. This has been referred to as "saturation theory" suggesting that the language related brain regions in patients with schizophrenia have less capacity to process normal auditory input. Furthermore, patients with schizophrenia showed less left- sided and more right-sided auditory cortical responses to external speech than healthy volunteers (reversed laterality). This could be interpreted as primary hyper-responsivity of the right temporal cortex and/or a compensatory increase due to dysfunction of the left temporal cortex (Woodruff, 2004). This illustrates how increased/reversed activity (in comparison with healthy volunteers) in one brain hemisphere may be associated with impaired function not only of that particular region, but also with regard to the opposite hemisphere. Although this lillustration is applicable to schizophrenia, it is possible that similar neurocircuitry in the **right mid-temporal region may be involved in the pathogenesis of auditory hallucinations in alcohol-induced psychotic disorder.**

As there were no areas demonstrated with significantly lower rCBF in patients with alcohol-psychotic disorder in comparison to healthy volunteers, post therapy activation may be less likely. Post-therapy activation (predominantly in the left frontal lobe) is however consistent with differences in rCBF shown in

comparison to the schizophrenia and alcohol dependent groups. Given the fact that chronic alcohol intake is associated with decreased frontal lobe perfusion (Moselhy et al, 2001), the **post-treatment increased perfusion demonstrated here may be consistent with post-abstinence improvement** (Gansler et al, 2000) and perhaps less likely a definite treatment effect. One particular area that could support this was found in the left basal ganglia. The cluster in the left putamen (MNI coordinates: -20,16,-4) had decreased rCBF compared to the alcohol dependence group. A cluster in the left caudate (MNI coordinates: -12,16,12) reported with increased post-treatment rCBF, share coordinates that may represent the same anatomical area. "Baseline-deactivation" was thus followed by post-treatment "normalisation". The possibility however also remains that anti-psychotic treatment exerting its dopamine-blocking effect in the basal ganglia contributed to this finding. Increased metabolic rates in the basal ganglia have been reported in response to treatment with haloperidol in patients with schizophrenia. A study by Buchsbaum et al (1992) demonstrated an association with clinical response, but another by Miller et al (1997) was unable to do so.

4.5 Conclusion of SPECT study

Baseline activation of rCBF of certain brain regions (including the superior medial aspect of the right frontal lobe, left pre-central frontal lobe, right pallidum and mid-region of right temporal lobe) distinguished this disorder from healthy volunteers. Reduced rCBF to the thalamus as suggested in previous case reports (Soyka et al, 2000a, 2000b, 2005 and Kitabayashi et al

2007) could not be confirmed. Increased rCBF to the left thalamus may explain previously reported asymmetric flow to the thalamus (Soyka et al 2005).

Only two significant and heterogeneous rCBF differences were demonstrated when comparing patients with alcohol-induced psychotic disorder with patients with schizophrenia, involving the left frontal and right mid-temporal lobes.

Heterogenous rCBF in alcohol-induced psychotic disorder was also evident but less prominent in comparison with alcohol dependence. The predominant finding was reduced comparative rCBF to portions of the left frontal lobe, the basal ganglia and the mid-temporal lobe bilaterally.

Areas that showed significant baseline activation **and** post-treatment de-activation and are likely to be involved in the pathogenesis of alcohol-induced psychotic disorder are the **left superior frontal lobe and the right mid-temporal/hippocampus region.**

As both post-treatment de-activation and activation were noted, it is postulated that areas associated with increased pre-treatment rCBF and post-treatment de-activation may reflect improvement more closely related to alcohol-induced psychotic disorder, whilst areas of post-treatment activation may be associated with a post-abstinence improvement effect.

4.6 Combined SPECT and Psychopathology (PANSS) study – Pre and Post Treatment correlations in Alcohol Induced Psychotic Disorder: Results

4.6.1 Demographics

The nineteen (n=19) participants (15 male, 4 female) with a mean (SD) age of 39 (4) years with alcohol-induced psychotic disorder that participated in the comparative baseline SPECT study were included and completed the 6-week treatment component of this study.

4.6.2 SPECT vs PANSS correlation results

4.6.2.1 Baseline correlations of rCBF and PANSS ratings in patients with Alcohol-induced Psychotic Disorder when assessing all brain areas.

The only significant positive correlation detected between rCBF and the PANSS at baseline was between the Positive scale of the PANSS and rCBF in the right cerebellum (table 15). Negative correlations were noted between the Negative, General and Total PANSS scales and rCBF in the right frontal lobe, the right occipital (fusiform) lobe, the right parietal lobe and the vermis of the cerebellum. Noticeably no correlations were detected in the left hemisphere of the brain. These results are summarised in tables 16-18.

Table 15. Positive correlation between rCBF and Positive PANSS at baseline

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
15	4.78	p<0.001	8,-80,16	Cerebellum R

(Height threshold: T=3.65, p=0.001)

Table 16. Negative correlation between rCBF and Negative PANSS at baseline)

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
11	4.8	p<0.001	40,-8,20	Rolandic Operculum R
13	4.45	p<0.001	20,-40,-12	Occipital Fusiform R
15	4.2	p<0.001	16,20,52	Frontal Sup R

(Height threshold: T=3.65, p=0.001)

Table 17. Negative correlation between rCBF and General PANSS at baseline.

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
13	4.72	p<0.001	40,-36,40	Supramarginal R
22	4.4	p<0.001	0,-40,-20	Cerebellum Vermis

(Height threshold: T=3.65, p=0.001)

Table 18. Negative correlation between rCBF and Total PANSS at baseline

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
21	4.86	p<0.001	12,20,48	Supplementary Motor Area R

(Height threshold: T=3.65, p=0.001)

4.6.2.2 Correlations of changes in rCBF and changes in PANSS ratings post vs pre treatment in patients with Alcohol-induced Psychotic Disorder when assessing all brain areas.

No significant correlations were detected **between changes in rCBF and ratings on the Positive scale of the PANSS** following pharmacotherapy.

Highly significant negative correlations were detected between changes in rCBF and changes on the Negative subscale of the PANSS following pharmacotherapy. These rCBF changes were predominantly in the left frontal lobe (6 clusters), the right frontal lobe (2 clusters), the parietal lobes, including the supramarginal regions bilaterally (3 clusters), the left temporal lobe, the left occipital lobe and the left cerebellum. (See table 19).

Table 19. Negative correlation between changes in rCBF and Negative PANSS following pharmacotherapy (activation).

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
33	5.89	p<0.001	-32,52,12	Frontal Mid L
51	5.64	p<0.001	36,16,32	Frontal Inf Operculum R
88	5.49	p<0.001	-28,-12,68	Frontal Pre Central L
94	5.32	p<0.001	-52,16,24	Frontal Inf Operculum L
50	5.28	p<0.001	32,44,20	Frontal Mid R
22	5.27	p<0.001	-56,-20,24	Parietal Supra Marginal L
72	4.9	p<0.001	-12,12,64	Supplementary Motor Area L
16	4.88	p<0.001	-8,48,28	Frontal Superior Medial L
10	4.87	p<0.001	-48,-20-24	Temporal Inferior L
43	4.68	p<0.001	44,-40,44	Parietal Supra Marginal R
16	4.66	p<0.001	-12,-60,-40	Cerebellum L
27	4.61	p<0.001	-28,-48,56	Parietal Inferior L
16	4.53	p<0.001	-20,-96,12	Occipital Mid L
10	4.0	p<0.001	-8,-24,36	Cingulum Mid L

(Height threshold: T=3.65, p=0.001)

Further negative correlations were evident when comparing changes in rCBF and changes on the **General subscale of the PANSS.** Significant changes correlated with **bilateral changes in rCBF in the temporal lobes (2 clusters each), the right frontal region (4 clusters), the left cerebellum, left thalamus and the right parietal lobe (precuneus)** (one cluster each). (See table 20.)

Table 20. Negative correlations between changes in rCBF and General PANSS following pharmacotherapy (activation).

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
61	6.32	p<0.001	-48,-16,4	Temporal Sup L
33	5.79	p<0.001	-12,-56,-40	Cerebellum L
16	5.51	p<0.001	-52,-20,-24	Temporal Inf L
43	5.5	p<0.001	-8,-20,20	Thalamus L
144	4.94	p<0.001	28,16,48	Frontal Mid R
22	4.89	p<0.001	28,-24,-8	Hippocampus R
35	4.87	p<0.001	44,-8,-28	Temporal Inf R
40	4.66	p<0.001	28,44,24	Frontal Mid R
29	4.66	p<0.001	12,-56,56	Parietal Precuneus R
10	4.63	p<0.001	4,-20,60	Supplementary Motor area R
12	4.62	p<0.001	52,-12,12	Rolandic Operculum R

(Height threshold: T=3.65, p=0.001)

The brain regions associated with significant negative correlations between changes in rCBF and changes on **the Total PANSS ratings** were the **temporal lobes (one cluster each bilaterally), the right frontal lobe (2 clusters) and the left parietal lobe and left cerebelum** with one cluster each. (See table 21.)

Table 21. Negative correlations between changes in rCBF and Total PANSS following pharmacotherapy (activation).

Cluster size (voxels)	T	p value	MNI coordinates (x,y,z)	Brain region
19	6.66	p<0.001	-52,-20,-24	Temporal Inf L
47	5.81	p<0.001	-56,-20,20	Parital Supramarginal L
63	5.29	p<0.001	36,12,28	Frontal Inf Operculum R
20	5.26	p<0.001	28,-24,-4	Hippocampus R
14	4.63	p<0.001	-12,-60,-44	Cerebellum L
10	4.02	p<0.001	28,44,20	Frontal Mid R

(Height threshold: T=3.65, p=0.001)

We failed to demonstrate any significant positive correlations between changes in rCBF and improvement on any of the PANSS rating scales.

4.7 Discussion of SPECT vs PANSS correlations

Significant correlations with change in rCBF and change on the various scales of the PANNS implicate involvement of the frontal, temporal, parietal and occipital lobes as well the cerebellum and the left thalamus in alcohol-induced psychotic disorder. No significant correlations were demonstrated between rCBF to the basal ganglia and any of the PANSS ratings.

4.7.1 Baseline correlations of Regional Cerebral Blood Flow (rCBF) and PANSS ratings in patients with Alcohol-induced Psychotic Disorder when assessing all brain areas.

In view of prominent individual item and total scores on the Positive subscale of the PANSS (see table 7) and significant baseline rCBF differences between patients with alcohol-induced psychotic disorder and healthy volunteers, significant baseline correlations were anticipated between these two

variables. **Only one significant correlation (positive) between baseline rCBF and the Positive subscale of the PANSS could however be detected, specifically in a portion of the right cerebellum.** Interesting is that **another cluster of the cerebellum (the vermis) showed a significant inverse correlation between baseline rCBF and the General subscale of the PANSS.** The explanation for these correlations is unclear. However, the cerebellum has been implicated in the pathogenesis of Wernicke's encephalopathy (cerebellar ataxia, opthalmoplegia and delirium) due to thiamine deficiency. Baker et al (1999) reported that thiamine-deficient patients with alcoholism had cerebellar changes that differed significantly from non-thiamine-deficient alcoholic patients. Thiamine-deficient alcoholic patients had significant decreases in Purkinje cell density and molecular layer volume in the cerebellar vermis suggesting selective vulnerability to thiamine deficiency in the cerebellum. Thiamine deficiency in alcoholic patients is also associated with reduced white matter volumes especially of the frontal and medial temporal lobes, but also of the thalamus (Krill et al 1997). Thiamine deficiency has thus far not been directly implicated in the develpment of alcohol-induced psychotic disorder but its potential role remains to be elucidated.

The role of the cerebellum has traditionally mainly been associated with motor coordination. It has however been shown that the cerebellum is also involved in neurocircuitry with links to pre-frontal, temporal and occipito-parietal association areas as well as the limbic system. Activation of the cerebellum has been demonstrated during cognitive tasks not related to movement as

reviewed by Bugalho et al 2006 and reduced cerebellar blood flow was associated with cognitive dysfunction in patients with chronic alcoholism (Melgaard et al 1990). Several authors have proposed a possible modulating role for the cerebellum in cognitive control (Rapoport et al 2000, Konarski et al, 2005, Bugalho et al, 2006 and Fusar-Poli et al, 2007), including a possible role in the pathogenesis of psychiatric disorders such as schizophrenia (Andersen, 2003). **A possible role for the cerebellum in alcohol-induced psychotic disorder therefore warrants further investigation.**

None of the sites associated with significant negative correlations between baseline rCBF and the Negative, General and Total subscales of the PANNS were followed by significant post-treatment correlations at that specific site. Significant correlations between baseline rCBF and the Negative subscale of the PANSS involving the **right frontal lobe** supports frontal lobe involvement in alcohol induced-psychotic disorder as discussed elsewhere in this paper.

4.7.2 Correlations of changes in Regional Cerebral Blood Flow (rCBF) and changes in PANSS ratings post vs pre treatment in patients with Alcohol-induced Psychotic Disorder when assessing all brain areas.

Hallucinations clinically constitute a prominent symptom in alcohol-induced-psychosis and are represented by item p3 in the **Positive subscale of the PANSS**. Although hallucinations were prominent in the cohort of patients with alcohol-induced psychotic disorder and significant symptom reductions were noted on both the p3 and Positive subscale of the PANSS**, we failed to demonstrate significant correlations between change in rCBF and**

improvement on the Positive subscale of the PANSS. Sabri et al (1997) encountered similar findings in a study involving never-treated patients with schizophrenia. Areas of hyperperfusion and hypoperfusion correllated exclusively with different positive symptoms, while the sumscore of of all the positive symptoms only correlated weakly with rCBF changes. This provides a possible explanation for failure to detect an equally strong correlation between changes in rCBF and changes on the positive PANSS subscale. It was suggested that different positive symptoms may produce opposite rCBF changes, thus cancelling out deviations. Individual symptom score correlations were not performed in this study, so that this possibility could not be further explored.

The absence of significant correlations between change in rCBF to the **basal ganglia** and any of the PANNS ratings is noteworthy. Anti-psychotic agents such as haloperidol exert its effects via meso-limbic, meso-cortical and nigro-striatal pathways. Any potential nigro-striatal therapeutic effects as measured by PANNS ratings and involving the basal ganglia may thus be interpreted as negligent or absent. This however also does not rule out possible individual symptom score correlations on the Positive subscale of the PANSS.

Improvement on the Negative subscale of the PANSS showed a number of highly significant negative correlations with change in rCBF post vs pre-therapy in patients with alcohol-induced psychotic disorder. The clusters involved were predominantly localized in the **frontal lobes**; six from the left and two from the right frontal lobe (see table 19). These findings were

unexpected in view of the fact that negative symptoms do not represent the core features of alcohol-induced psychotic disorder. Also, baseline negative symptom scores were low in our sample. Furthermore, we did not find statistical significant improvement on the Negative subscale of the PANSS when assessing psychopathology independently from change in rCBF (see psychopathology section). Nevertheless, we found individual items on the Negative subscale that demonstrated significant improvement after treatment. These were the items representing emotional withdrawal (item n2), passive/apathetic social withdrawal (item n4) and stereotyped thinking (item n7).

These improvements are unlikely due to anti-psychotic treatment alone. It is quite plausible to consider that these correlations may also represent a post-treatment abstinence improvement effect given the fact that frontal brain perfusion abnormalities may subside with extended abstinence (Gansler et al, 2000). As the changes on the Negative subscale of the PANSS were score reductions (improvement), these negative correlations with change of rCBF are likely to reflect post-therapy increase of rCBF.

Rosse et al (1997) found a significant relationship between frontal lobe pathology as measured by CT and negative symptoms measured by the Negative Scale of the PANSS in patients with chronic alcoholism. We noted three regions of the left frontal lobe that showed both significant increased rCBF post vs pre therapy and change of rCBF that correlated significantly negatively with change (improvement) on the Negative subscale of the

PANSS. These areas were the **left supplementary motor area** (MNI coordinates: -8,0,68 and -12,12,64), the **left pre-central region** (MNI coordinates: -24,-24,64 and -28,-12,68) and the **mid cingulum** (MNI coordinates: 0,-12,40 and -8,-24,36). Each set of two MNI coordinates represent a cluster close enough to represent one anatomical area (< 20mm apart). Noticeably no other brain region demonstrated this combination of findings. Though it was difficult to verify, most of our patients reported abstinence during the study.

We therefore postulate that these frontal lobe rCBF changes correlating significantly negatively with changes on the Negative subscale of the PANSS may represent improvement subsequent to extended abstinence from alcohol.

Of particular interest are two anatomical areas in the left frontal lobe each represented by two clusters, less than 20mm apart, that displayed both significant increased baseline rCBF vs volunteers (as reported in the previous section) and change of rCBF post vs pre therapy correlating significantly negatively with change on the Negative subscale of the PANSS. These areas were located in the **left mid frontal lobe** (MNI coordinates: -24,48,8 and -32,52,12) and an area associated with the **deep central region and inferior operculum of the left frontal lobe** (MNI coordinates:-44,0,24 and -52,16,24). We previously reported two other areas that were associated with significant increased baseline rCBF vs volunteers and post-therapy de-activation. This finding indicates that increased baseline rCBF vs volunteers may also be

associated with change of rCBF post vs pre therapy correlating significantly negatively with change on the Negative subscale of the PANSS in specific anatomical areas.

A possible explanation is that baseline rCBF activation could be followed by post-treatment rCBF activation in some areas, as both post-treatment activation and de-activation were demonstrated in the previous section. **Evidence also points to post-treatment activation as a rCBF feature associated with clinical improvement.** This is supported by significant negative correlations between improvement on the Negative, General and Total PANSS scores and the absence of any positive correlations between improvement on any of the PANSS rating scales and change of rCBF. It is further postulated that some areas of activation may represent compensatory mechanisms for areas of de-activation elsewhere. This is also consistent with the possibility that post-treatment activation represents post-abstinence improvement as suggested earlier.

Three anatomical areas demonstrated significant negative correlations between changes of rCBF and simultaneous improvement on the Negative, General and Total PANSS scores. (Note that the Negative and General scores are included in the Total PANSS score). The three areas were located in the **right mid frontal lobe** (MNI coordinates: 28,44,24 and 28,44,20 and 32,44,20), **the left inferior temporal lobe** (MNI coordinates: -48,-20,-24 and -52,-20,-24 and -52-20,-24) and the **left cerebellum** (MNI coordinates: -12,-60,-44 and -12,-60,-40 and -12,-56,-40). Each of these three areas were

represented by 3 sets of coordinates that represented clusters that were less than 20mm apart. A likely interpretation is that the Negative and General subscales of the PANSS share related items/symptoms that are simultaneously operative in the improvement of alcohol-induced psychotic disorder at these locations. Similarly, it also supports the notion that these structures are involved in the pathogenesis of alcohol-induced psychotic disorder.

Given the pharmacodynamic action of haloperidol exerting its therapeutic action on D2 receptors in mesocortical and mesolimbic pathways involving the frontal and temporal lobes, we postulate that changes in rCBF involving these structures and that correlate with clinical improvement, may also reflect a **pharmacological treatment effect**.

Assessment of parietal lobe rCBF was not included in the comparative SPECT study. Change of rCBF to the **parietal lobes** however showed significant negative correlations with improvement on the various scales in the treatment study. These included rCBF changes to the right precuneus region and bilateral supramarginal regions of the parietal lobes. Change of rCBF to the left supramarginal area was represented by two almost identical clusters that showed significant negative correlations with improvement on both the Negative and the Total PANSS scores. A lesion affecting the supramarginal area is usually associated with hemi-neglect. The left tempero-parietal cortex (including the supramarginal region) is however also involved in phonological retrieval and a deficit may be associated with interference with “inner speech”

(Shergill et al 2001). Our findings suggest that it may play a role in alcohol-induced psychotic disorder, especially if one considers a possible association with symptoms such as auditory hallucinations. Noteworthy is that diminished regional cerebral glucose utilization in the left parietal lobe (Martin et al, 1992) and precuneus (Joyce et al, 1994) have been reported in patients with alcoholism and Wernicke-Korsakoff's syndrome respectively.

The negative correlation detected between change in rCBF in the left thalamus and improvement on the General PANSS is consistent with previous reported **impairment of thalamic function** in alcohol induced-psychotic disorder. Our findings suggest that left thalamic involvement may explain the asymmetric thalamic metabolism reported by Soyka et al 2005.

One site in the right occipital lobe showed a significant inverse correlation between baseline rCBF and the Negative subscale of the PANSS. Another site in the left occipiatal lobe showed a significant correlation between change of rCBF and improvement on the Negative subscale of the PANSS. The possibility is that this reflects a relative post-therapy increase of rCBF to left occipital lobe. Occipital lobe dysfunction in this disorder may explain the occasional occurrence of visual hallucinations in alcohol-induced psychotic disorder.

4.8 Conclusion of Treatment Study

Significant negative correlations between change in rCBF and improvement on Negative, General and Total PANSS ratings, support our earlier finding

which implicate dysfunction of the the frontal and temporal lobes as well as the thalamus in alcohol-induced psychotic disorder. Further evidence also points towards involvement of the parietal and occipital lobes and the cerebellum. Basal ganglia involvement could not be confirmed in this component of the study. The lack of significant correlations between change in rCBF and the Positive subscale of the PANSS may not reflect possible correlations between rCBF and individual items of the Positive subscale.

Although treatment effects were demonstrated, we were unable to distinguish between pharmacological effects and the possible improvement accomplished by abstinence from alcohol. However, a treatment effect is suggested by the fact that the majority of patients previously had relapsing psychotic features clearly associated with alcohol intoxication and/or withdrawal that did not clear upon abstinence prior to entering the treatment study. We postulate that both mechanisms could be simultaneously operative.

Negative correlations between rCBF changes and change on the various PANSS scales point to post-treatment activation as a rCBF feature associated with clinical improvement.

5. FINAL CONCLUSIONS

This study provides further supportive evidence for the view that alcohol-induced psychotic disorder can be distinguished from schizophrenia. Our findings confirmed that the **age of onset** of alcohol-induced psychotic disorder is higher than that of schizophrenia (Soyka, 1990). Evidence from our cohort also points to a **lower pre-morbid educational level** in the alcohol-induced psychotic disorder group. Along with the **mild cognitive impairment** detected in comparison with healthy volunteers and alcohol dependent patients, it may be indicative of a possible developmental risk factor.

We were unable to confirm a greater **degree of alcohol dependence** in this disorder. As concomitant substance abuse was an exclusion criterion in this study, we are of the opinion that other substance abuse is not an essential risk factor for the development of this disorder.

Co-morbid anxiety and depressive symptoms were noted significantly more in the alcohol-induced psychotic disorder group compared to the schizophrenia group. Our findings suggest that these symptoms represent features of alcohol-induced psychotic disorder rather than independent anxiety or depressive disorders. Whether the high rate of suicidal behaviour reported by patients with alcohol-induced psychotic disorder (35.7%) and noted in other studies (Soyka et al, 1988) is a reflection of anxiety, depression or psychosis or a combination there of, remains to be determined.

Patients with alcohol-induced psychotic disorder presented with significantly **less severe psychotic features, better jugdement, insight and awareness of their condition and less functional impairment** than patients with schizophrenia. In addition, we found virtualy no evidence of thought process disorder in our cohort of patients with alcohol-induced psychotic disorder. Negative symptoms as measured by the negative scale of the PANSS and generally associated with a negative symptom syndrome in schizophrenia, were significantly milder in the alcohol-induced psychotic disorder patients compared to the schizophrenia group. Notwithstanding these low ratings and lack of significant improvement noted on the negative scale of the PANSS post-therapy, improvement of these symptoms correlated significantly with change in rCBF to predominantly the frontal lobes in patients with alcohol-induced psychotic disorder. The explanation of these findings is not clear. Looking at the post-therapy improvement of **individual items** on the negative scale of the PANSS, we found that **three items** (item 2, emotional withdrawal; item 4, passive social withdrawal and item 7, stereotyped thinking) showed significant post-therapy improvement whilst **four items** (item 1, blunted affect; item 3, poor rapport; item 5, poor abstract thinking and item 7, stereotyped thinking) did not show significant improvement. It remains possible that improvement of the three individual symptom items were responsible for the correlation with significant changes noted in rCBF post therapy. Taking in account that these individual items do not include psychotic symptoms of alcohol-induced psychotic disorder, we would argue that it is more likely that these symptoms did not improve due to anti-psychotic treatment (alone) but rather improved due to abstinence from alcohol. It is further postulated that a

lack of significant improvement on the negative scale of the PANSS may be indicative of relatively chronic symptoms associated with alcoholism.

The significant improvement noted on the positive, general and total scales of the PANSS is consistent with previous reports (Johannson, 1961; Glass, 1989 and Soyka, 1990) indicating reversibility and **good prognosis** of alcohol-induced psychotic disorder providing abstinence is maintained.

Significant differences in baseline rCBF between patients with alcohol-induced psychotic disorder and patients with **schizophrenia** were also demonstrated in the baseline SPECT study. Higher and lower rCBF in patients with alcohol-induced psychotic disorder were noted to the right mid temporal and left frontal lobes respectively. We indicated that the likelihood exists that the right mid-temporal region be similarly involved in the pathogenesis of auditory hallucinations in alcohol-induced psychotic disorder as in schizophrenia. No significant differences could however be demonstrated between baseline thalamic and striatal rCBF of these two patient groups. Our findings do not exclude some possible shared biological substrate between these disorders.

Significantly higher baseline rCBF to especially the medial aspect of the right and pre-central aspect of the left frontal lobes, but also to the right pallidum, mid-region of the right temporal lobe and left thalamus distinguished this disorder from **healthy volunteers**. Although the asymmetrical rCBF noted to the thalamus was consistent with previous reports, reduced rCBF to the

thalamus could not be confirmed. Increased rCBF to certain portions of the temporal cortex in patients with alcohol-induced psychotic disorder and previously reported in patients with alcohol-withdrawal, may point towards mutually impaired neuronal mechanisms contributing to the pathogenesis of the two alcohol-related disorders.

Heterogeneous rCBF was also noted in the alcohol-induced psychotic disorder group in comparison with **alcohol dependent** patients, the predominant findings being reduced comparative rCBF to portions of the left frontal lobe, the basal ganglia and the mid-temporal lobe bilaterally.

Both post-treatment de-activation and activation were noted. We postulate that areas associated with increased pre-treatment rCBF and post-treatment de-activation (eg. the left superior frontal lobe and right mid-temporal /hippocampus region) reflect improvement of alcohol-induced psychotic disorder, whilst areas of post-treatment activation (eg. left supplementary motor area, left caudate and left Rolandic operculum) may reflect an improvement due to abstinence from alcohol.

Significant positive and inverse correlations between the positive and general subscales of the PANSS respectively and rCBF to cerebellar regions, implicate the **cerebellum and possibly thiamine deficiency** as having possible roles in the pathogenesis of alcohol-induced psychotic disorder. These findings warrant further investigation.

Whilst we failed to demonstrate significant correlations between change in rCBF and improvement on the positive subscale of the PANSS, we suggest that individual positive subscale item symptoms may produce opposite rCBF changes, thus possibly cancelling out deviations. Assessment of individual item correlations with rCBF changes did not fall into the scope of this study, but further exploration of these data is envisaged. Changes in the basal ganglia could not be associated with a significant improvement effect. We believe that this may be due to the same methodological discrepancy.

Evidence indicating that changes in specific frontal, temporal, parietal, occipital, thalamic and cerebellar rCBF showed significant negative correlations with improvement on the negative, general and total PANSS ratings, implies dysfunction of these areas in alcohol-induced psychotic disorder. Although treatment effects were demonstrated, we were unable to distinguish between pharmacological effects and the possible improvement accomplished by abstinence from alcohol. We postulate that both mechanisms are simultaneously operative.

Although demonstration of possible dysfunctional anatomical brain regions may imply the existence of focal brain abnormalities, evidence point towards a “dysfunctional network” in alcohol-induced psychotic disorder rather than a “single aberrant centre”, as also postulated in schizophrenia (Shergill, Cameron et al 2001; David, 2004, Stephan et al 2006).

5.1 Limitations and future directions

Interpretation of some results may have limitations due to small sample sizes and disproportion of gender. In the SPECT studies there were disproportions of women in the schizophrenia (higher) and in the alcohol dependent (lower) groups compared to the alcohol-induced psychotic disorder group respectively. A certain amount of selection bias may have preceded the study in view of the exclusion of disorders (eg. comorbid mood and anxiety disorders) that may arguably contribute to the pathogenesis of the disorder. Though our patients did not suffer from primary mood and or anxiety disorders, future studies may need to uitilize a control design to assess the potential role of such disorders.

Although serious efforts were made to exclude substance related disorders, negative screening could not rule out subsequent use during the course of the study. Cigarette smoking (which was not disallowed) during the study in combination with alcohol use disorders may also affect brain perfusion particularly to the frontal lobes (Durazzo et al, 2007). Similar efforts were made to exclude comorbid general medical disorders. HIV-serology and EEG assessments were however not performed. The treatment arm of this study lacked a double-blind controlled study design. It was difficult to guarantee sobriety amongst patients after initiation of the study, thus possibly confounding treatment effects. Future studies may therefore need to address these factors.

Nevertheless, the results of this study are encouraging, particularly because to our knowledge, this is one of the few prospective studies and the first documented neuro-imaging study in alcohol-induced psychotic disorder. Previous neuro-imaging reports were based on case reports. Specific emphasis is made of the prospective design of this study that utilized standardized ratings scales, MRI brain scanning and drug screening procedures to allow for amongst others exclusion of comorbid neuro-psychiatric conditions and substance abuse.

The role of other brain regions such as the parietal lobes and cerebellum as well as possible etiological factors such as thiamine deficiency warrant further research. Placebo-controlled research specifically designed to distinguish between the effect of medication vs the role of abstinence from alcohol would be worth exploring. SPECT studies are generally unable to distinguish between changes in rCBF due to atrophy and other causes. Cerebral atrophy may thus have inluenced SPECT findings. Research correlating functional and structural neuroimaging would therefore also be worth exploring.

While there is little evidence that dopamine receptor dysfunction contributes to this disorder, the role of dopamine transporter may yet provide additional information to the current SPECT findings. (Soyka et al, 2000a).

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7. ACKNOWLEDGEMENTS

I wish to thank my promotor Prof. Robin Emsley and co-investigators Dr. James Warwick, Prof's. Richard Hewlett, Ben van Heerden and Daan Nel (statistician) for invaluable advice and assistance.

I am grateful to all my colleagues including Paul Carey, Yumna Dhansay, Mickey Gerber, Melany Hendricks, Willie Pienaar, Mimi Roberts, Sorya Seedat, Retha Smit, Helena Thornton and Thania van Greunen as well as to nursing, nuclear medicine, radiography and administrative staff at Tygerberg campus and Tygerberg, Stikland and Christiaan Barnard Memorial Hospitals who supported me directly or indirectly with encouragement, advice and assistance during the study.

My wife Louisa has been a wonderful source of motivation and encouragement. My children Juhan and Lorraine have made sacrifices some of which they may yet be unaware of. I owe much appreciation to my parents Jurie and Annatjie and to my sister Alida, for inspiration and support ever since I can remember.

The study was financed by funding from the Harry Crossley Foundation as well as from research assistant funds provided by the University of Stellenbosch. It is with much appreciation that I thank all participants including patients and healthy volunteers, but above all, the Almighty, who made this study possible.

Appendix A

Substance (alcohol)-induced Psychotic Disorder (DSM IV-TR, 2000):

A. Prominent hallucinations or delusions. Note. Do not include hallucinations if the person has insight that they are substance induced.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2) :

(1) the symptoms in Criterion A developed during, or within a month of substance intoxication or withdrawal

(2) medication use is etiologically related to the disturbance

C. The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following: the symptoms precede the onset of substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent non-substance-related episodes).

D. The disorder does not occur exclusively during the course of a delirium.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Code: [Specific Substance] – Induced Psychotic Disorder:
(Alcohol-Induced Psychotic Disorder with Delusions; Alcohol-Induced Psychotic Disorder with Hallucinations.)

Specify if:
With onset during intoxication: if criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome.
With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome.

Appendix B

Psychotic Disorder due to the use of Alcohol (ICD-10, 1993)

A. Onset of psychotic symptoms must occur during or within 2 weeks of substance use.

B. The psychotic symptoms must persist for for more than 48 hours.

C. Duration of the disorder must not exceed 6 months.

The diagnosis of psychotic disorder may be further specified by using the following:

Schizophrenia-like

Predominantly delusional

Predominantly hallucinatory

Predominantly polymorphic

Predominantly depressive symptoms

Predominantly manic symptoms

Mixed

For research purposes it is recommended that change of the disorder from a non-psychotic to a clearly psychotic state be further specified as either abrupt (onset within 48 hours) or acute (onset in more than 48 hours but les than 2 weeks).

Late-onset Psychotic Disorder due to Alcohol use (ICD-10)

A. Conditions and disorders meeting the criteria for the individual syndrome should be clearly related to the substance use. Where the onset of the condition or disorder occurs subsequent to use of psychoactive substances, strong evidence should be provided to demonstrate a link.

B. The general criteria for psychotic disorder must be met, except with regard to the onset of the disorder, which is more than 2 weeks but not more than 6 weeks after substance use.

Appendix C

ALKOHOL–GEïNDUSEERDE PSIGOSE STUDIE

PASIëNTINLIGTINGSTUK EN TOESTEMMINGSVORM

Hierdie inligtingstuk is saamgestel om dit vir u moontlik te maak om vrylik te besluit of u aan hierdie studie wil deelneem. Lees asb. sorgvuldig.

Wat is die doel van die studie?

U word gevra om vrywillig deel te neem aan ‘n studie wat breinfunksie in 3 verskillende toestande (alkoholgeïnduseerde psigose, alkoholafhanklikheid en skisofrenie) met normale kontrole gevalle vergelyk.

Indien u ly aan alkohol-geïnduseerde psigose sal u ook gevra word om deel te neem aan ‘n 6 weke behandelingstudie met toepaslike medikasie vir u toestand. Tydens hierdie tydperk sal van u verwag word om nie ander medikasie, alkohol of substanse te neem nie.

Wat word van my verwag tydens die studie?

As u deelneem aan die studie sal die dokter u bloeddruk, pols en gewig meet en fisies ondersoek. Hy sal u vra om vrae tydens die afneem van ‘n gestruktureerde psigiatriese onderhoud te beantwoord. U sal ook gevra word om bloed (omtrent 5-10ml of 2-4 teelepels) en uriene monsters te verskaf vir toksikologiese sifting. Daar sal gereël word dat u ‘n breinbeeldingstoets (SPECT) en 'n magnetiese resonansie (MR) studie van die brein ondergaan. Indien u diagnose alkoholgeïnduseerde psigose is, sal u gevra word om u medikasie gereeld te neem en 2 verdere afsprake tydens (na 3 weke) en aan

die einde van die studie (na 6 weke) na te kom. Na afloop van die studie sal u weer dieselfde toetse (behalwe die MR studie) ondergaan.

Wat behels die psigiatriese onderhoud?

Die ondersoeker sal vrae aan u stel volgens vasgestelde psigiatriese vraelyste. Dit behels gewoonlik soortgelyke vrae as wat u reeds by u eie psigiater beantwoord het.

Wat behels die SPECT studie?

Die SPECT studie behels 'n beelding studie van die brein. Dit is 'n tipe breinskandering ("brain scan"), maar behels dat u 'n lae dosering radio-aktiewe middel ingespuit word om die beeld van die brein te versterk. **Die hoeveelheid bestraling wat u sal ontvang, is ongeveer gelyk aan die dosis betrokke by 'n koronêre angiogram (bloedvatstudie).** Indien u twee sulke studies sal ondergaan, is **die stralingsdosis ongeveer dieselfde of ietwat meer as wat ‘n persoon wat met met bestraling werk per jaar mag ontvang.** U sal gevra word om vir ten minste 30 minute stil te lê vir hierdie toets. Voor die inspuiting sal u ‘n klein hoeveelheid bitter vloeistof moet drink om opname van die radio-aktiewe middel in die speekselkliere te beperk.

Wat behels die MR studie?

Hierdie studie behels ook breinbeelding, maar benodig geen inspuiting nie en behels ook nie die gebruik van bestraling nie.

Vervoerreëlings

Privaatvervoer na die SPECT studie (Tygerberghospitaal) en MR studie (City Park Hospitaal) sal kosteloos verskaf word.

Wat behels die medikasie?

Die medikasie wat aan u voorgeskryf sal word, is 'n geregistreerde medikament wat die simptome wat u ondervind behoort te verbeter. U sal die medikasie daagliks gebruik in een tot twee maal per dag doserings. Dit is 'n veilige middel, maar kan soms newe-effekte veroorsaak. Die mees algemene newe-effekte is bewerigheid, styfheid, sedasie en rusteloosheid. Onwillekeurige bewegings kom minder dikwels voor. 'n Seldsame ernstige toestand wat koors en spierstyfheid tot gevolg kan hê, kan gewoonlik met vroegtydige onttrekking van die medikasie en ondersteunende behandeling doeltreffend behandel word. Indien u spierstyfheid ondervind, moet u dit aan die dokter rapporteer, wat voorkomende medikasie daarvoor sal oorweeg.

Is daar alternatiewe medikasie beskikbaar?

Daar is alternatiewe medikasie beskikbaar, maar dit het gewoonlik soortgelyke effekte en newe-effekte as die wat met die studie beoog word.

Is daar enige voordele?

U simptome mag tydens die verloop van die studie opklaar. U sal geen onkoste hê met betrekking tot die ondersoeke of medikasie nie.

Is die studie eties aanvaarbaar?

Die studie is goedgekeur deur die Navorsingskomitee van die Universiteit van Stellenbosch se Mediese Fakulteit

Vertroulikheid?

Die gewone vertroulikheid tussen dokter en pasiënt sal gehandhaaf word, maar die bevindings van die studie sal bekend gemaak word sonder om u identiteit te openbaar.

Kan ek onttrek tydens die studie?

U besluit om aan die studie deel te neem, beïnvloed nie u verhouding met u dokter of hierdie hospitaal nie. Indien u sou wou onttrek, staan dit u vry om sonder nagevolge te onttrek, net soos wat dit die dokter vry staan om u van die studie te onttrek indien u nie baat vind daarby nie.

As u besluit om aan die studie deel te neem, moet u u algemene praktisyn daarvan in kennis stel.

Indien u iemand benodig tydens die studie, kan u die volgende persoon skakel :

Naam:.....

Telefoonnommer:.....

.

Die ondersoekende dokter sal enige vrae wat u mag hê beantwoord. As u besluit om aan die studie deel te neem, moet u hieronder daarvoor teken:

Ek, die ondergetekende, ..., het die inligtingstuk gelees en het die inligting wat ek benodig van die ondersoekende dokter verkry en gee hiermee my vrywillige toestemming om aan hierdie studie (alkohol-geïnduseerde psigose) deel te neem.

Pasiënt se Naam:.....

Handtekening:.....

Ondersoeker se Naam:.....

Handtekening: .....

Getuie se Naam: .....

Handtekening :.....

Datum:.....

Appendix D

ALCOHOL INDUCED PSYCHOSIS STUDY

PATIENT INFORMATION AND INFORMED CONSENT

These guidelines has been compiled to enable you to freely decide whether or not to participate in this study. Please read carefully.

What is the aim of the study?

You are requested to participate voluntarily in a study that will compare brain function in 3 different disorders (alcohol induced psychosis, alcohol dependence and schizophrenia) to that of normal control cases.

If you suffer from alcohol induced psychosis, you will also be requested to participate in a 6 week treatment study with appropriate medication for your condition. During this period it would be requested from you not to use other medication, alcohol or drugs.

What is expected from me during the study?

Should you participate in this study, the doctor will measure your blood pressure, pulse rate and weight and he will examine you physically. He will ask you various questions during the course of a structured psychiatric interview. You will also be requested to allow blood (about 5-10ml or 2-4 teaspoons) and urine sampling for toxicological screening.

It will also be arranged that you undergo a brain imaging study (SPECT) and a magnetic resonance imaging (MRI) study of the brain.

Should you have a diagnosis of alcohol-induced psychosis, you will be requested to take your medication regularly and to attend two further appointments during the course (after 3 weeks) and after the study (6 weeks). At the end of the study, you will complete the same tests (except the MRI study).

What does the psychiatric interview involve?

The investigator will ask various questions according to standard psychiatric questionnaires. It would be similar to the questions that are usually asked by a psychiatrist.

What is a SPECT study?

The SPECT study involves an imaging study of the brain. It is similar to an ordinary brain scan, but involves the injection of a low dosage radio-active substance to amplify the picture of the brain. **The amount of radiation you will receive is equivalent to that received during a coronary angiogram.** In subjects where two SPECT studies will be performed, the total amount of radiation received by each subject **will be about the same or slightly more than the yearly permissible dose for a radiation worker.** You will be asked to lie still for at least 30 minutes for this test. **Before the injection you will be requested to drink a small amount of bitter tasting liquid to minimise uptake of the radio-active substance in the salivary glands.**

What does the MR study consist of?

This is also a brain imaging study but does not require any injection and does not involve any radiation.

Transport Arrangements

Private transport will be arranged to the SPECT study (Tygerberg Hospital) and the MRI study (City Park Hospital) at no further costs.

What does the medication consist of?

The prescribed medication is registered medicine that should improve the symptoms that you are experiencing. You will use the medication daily in once to twice daily dosages. It is safe medicine but may sometimes produce side-effects. The most common adverse effects are tremors, rigidity, restlessness and sedation. Involuntary movements occur less frequently. An uncommon serious condition that may cause fever and rigidity, can usually be reversed by early withdrawal of medication and supportive management. Should you experience muscle stiffness, you should report it to your doctor who would consider preventative medication for the treatment thereof.

Are there alternative treatments available?

There is alternative medication available, but it has similar side effects to the one proposed for this study.

Would there be any advantages?

Your symptoms may improve during the course of the study. You will have no costs with regard to investigations or medication.

Has the study been ethically approved?

The study has been approved by the Research committee of the Medical Faculty of the University of Stellenbosch.

Confidentiality?

The usual confidentiality between practitioner and patient will be adhered to, but the results of the study will be made public without it being possible to identify you in any possible way.

May I withdraw from the trial once it has started?

Your decision to participate in this study, does not influence your relation with the doctor or this hospital. Should you wish to withdraw, you are entitled to leave without negative consequences. Likewise the doctor may decide that you leave the study, should it be unlikely that you will benefit from further participation.

If you decide to participate in the study, you need to inform your general practitioner.

Should you need someone during the course of the study, you may contact the following person:

Name:.....

Telephone Number.....

The investigating doctor will answer all questions that you may have. Should you decide to paricipate in this study, you have to sign below :

I, the undersigned, ..., have read the information sheet and obtained the necessary information from the investigating doctor and hereby give my freely obtained consent to participate in this study (alcohol induced psychosis).

Name of Patient:.....

Signature:.....

Name of Investigator .....

Signature: .....

Name of Witness:.....

Signature:.....

Date:.....

Appendix E

Rating scales and clinical research instruments

Agitated Behavior Scale (ABS)

Calgary Depression Scale for Schizophrenia (CDSS)

Clinical Global Impression of Severity of Psychosis (CGI-SP)

Hamilton Depression Rating Scale (Ham-D)

Hamilton Anxiety Rating Scale (Ham-A)

Mini-Mental State Examination (MMSE)

Positive and Negative Syndrome Scale (PANSS)

Scale of Functioning (SOF)

Scale to assess unawareness of mental disorder (SUMD)

Severity of Alcohol Dependence Questionnairre (SADQ)

Appendix F

SUMMARY OF CHANGES IN REGIONAL CEREBRAL BLOOD FLOW IN PATIENTS WITH ALCOHOL-INDUCED PSYCHOTIC DISORDER : (Table 22)

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Frontal Lobe (Left)		
Superior Medial	(-8,48,28)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Superior	(-16,36,36)	Increased rCBF vs volunteers (p<0.01)
	(-20,32,32)	Decreased rCBF post vs pre therapy (p<0.01)
Middle	(-32,52,12)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(-24,48,8)	Increased rCBF vs volunteers (p<0.01)
Middle	(-36,24,52)	Decreased rCBF vs alcohol dependent group (p<0.01)
Inferior Operculum	(-52,16,24)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Inferior Tri	(-32,12,28)	Decreased rCBF vs schizophrenia group (p<0.001)
	(-44,20,20)	Decreased rCBF vs alcohol dependence group (p<0.01)
Inferior Orbital	(-40,28,-16)	Decreased rCBF post vs pre therapy (p<0.01)
	(-40,40,-4)	Decreased rCBF vs alcohol dependence group (p<0.001)
Mid Orbital	(-20,52,-20)	Decreased rCBF post vs pre therapy (p<0.01)
Supplementary Motor Area	(-8,0,68)	Increased rCBF post vs pre therapy (p<0.001)
	(-12,12,64)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Rolandic Operculum	(-48,-20,20)	Increased rCBF post vs pre therapy (p<0.001)
Pre central	(-24,-24,64)	Increased rCBF post vs pre therapy (p<0.01)
	(-28,-12,68)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Deep to Pre central	(-44,0,24)	Increased rCBF vs volunteers (p<.001)
Cingulum Mid	(0,-12,40)	Increased rCBF post vs pre therapy (p<0.01)
	(-8,-24,36)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)

Appendix F (table 22) continued

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Frontal Lobe (Right)		
Superior Medial	(16,52,8)	Increased rCBF vs volunteer group (p<0.001)
Superior	(16,40,44)	Decreased rCBF vs alcohol dependence group (p<0.01)
	(16,20,52)	Decreased rCBF at baseline correlating with Negative PANSS (p<0.001)
Supplementary Motor Area	(12,20,48)	Decreased rCBF at baseline correlating with Total PANSS (p<0.001)
	(4,-20,60)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
Superior Orbital	(16,32,-20)	Decreased rCBF vs alcohol dependence group (p<0.01)
Mid Orbital	(36,52,-12)	Decreased rCBF post vs pre therapy (p<0.01)
Rolandic Operculum	(40,-8,20)	Decreased rCBF at baseline correlating with Negative PANSS (p<0.001)
	(52,-12,12)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
Inferior Operculum	(36,16,32)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(36,12,28)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
Middle	(28,16,48)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
	(28,44,24)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
	(28,44,20)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
	(32,44,20)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)

Appendix F (table 22) continued

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Temporal Lobe (Left)		
Superior	(-48,-16,4)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
Middle	(-56,-56,4)	Decreased rCBF vs alcohol dependent group (p<0.01)
	(-48,-48,0)	Increased rCBF vs volunteer group (p<0.01)
Inferior	(-44,4,-28)	Increased rCBF vs volunteer group (p<0.01)
	(-48,-20,-24)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(-52,-20,-24)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
	(-52,-20,-24)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
Parahippocampus	(-12,4,-20)	Increased rCBF vs alcohol dependent group (p<0.01)

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Temporal Lobe (Right)		
Middle	(48,-56,0)	Increased rCBF vs volunteer group (p<0.01)
	(56,-44,-4)	Decreased rCBF vs alcohol dependent group (p<0.01)
	(52,-64,24)	Increased rCBF vs schizophrenia group (p<0.01)
	(36,8,-28)	Increased rCBF vs volunteer group (p<0.01)
Hippocampus	(40,-20,-8)	Decreased rCBF post vs pre-treatment (p<0.01)
Near hippocampus	(40,-4,-20)	Decreased rCBF post vs pre-treatment (p<0.01)
Hippocampus	(28,-24,-8)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
	(28,-24,-4)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
Inferior	(44,-8,-28)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)

Appendix F (table 22) continued

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Basal ganglia (Left)		
Putamen	(-20,16,-4)	Decreased rCBF vs alcohol dependence group (p<0.001)
Caudate	(-12,16,12)	Increased rCBF post vs pre treatment (p<0.001)
Basal ganglia (Right)		
Caudate	(20,24,4)	Decreased rCBF vs alcohol dependence group (p<0.01)
Pallidum	(16,-4,0)	Increased rCBF vs volunteer group (p<0.01)

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Thalamus (Left)		
Thalamus	(-16,-12,-4)	Increased rCBF vs volunteer group (p<0.01)
Thalamus	(-8,-20,20)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
Thalamus (Right)	n/a	No correlations found

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Parietal Lobe (Left)		
Inferior	(-28.-48.56)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Supramarginal	(-56,-20,24)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(-56,-20,20)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
Parietal Lobe (Right)		
Supramarginal	(44,-40,44)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(40,-36,40)	Decreased rCBF at baseline correlating with General PANSS (p<0.001)
Precuneus	(12,-56,56)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)

Appendix F (table 22) continued

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Occipital Lobe (Left)		
Middle	(-20,-96,12)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
Occipital Lobe (Right)		
Inferior (fusiform)	(20,-40,-12)	Decreased rCBF at baseline correlating with Negative PANSS (p<0.001)

Brain Region	MNI coordinates (x,y,z)	Regional Cerebral Blood Flow (rCBF)
Cerebellum (Left)		
Cerebellum	(-12,-60,-44)	Negative correlation between change in rCBF and change in Total PANSS post vs pre therapy (p<0.001)
	(-12,-60,-40)	Negative correlation between change in rCBF and change in Negative PANSS post vs pre therapy (p<0.001)
	(-12,-56,-40)	Negative correlation between change in rCBF and change in General PANSS post vs pre therapy (p<0.001)
Cerebellum (Centre)		
Vermis	(0,-40,-20)	Decreased rCBF at baseline correlating with General PANSS (p<0.001)
Cerebellum (Right)		
Cerebellum	(8,-80,16)	Increased rCBF at baseline correlating with Positive PANSS (p<0.001)