SPECT SCINTIGRAPHIC Tc-99m HMPAO APPEARANCE IN PRE-AND POST ELECTROCONVULSIVE THERAPY (ECT) IN PATIENTS WITH MAJOR DEPRESSION.

M.D.T.H. VANGU

Johannesburg, 1998

SPECT SCINTIGRAPHIC Tc-99m HMPAO APPEARANCE IN PRE- AND POST-ELECTROCONVULSIVE THERAPY (ECT) IN PATIENTS WITH MAJOR DEPRESSION

M.D.T.H. VANGU

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine (Nuclear Medicine)

Johannesburg, 1998.

DECLARATION

I declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

M.D.T.H. VANGU

26.02.98

Date

This research was approved by the committee for Research on Human Subjects, University of the Witwatersrand (protocol #M960920) and was carried out in the Department of Nuclear Medicine, University of the Witwatersrand in 1997.

To my late father, pilot Jean-Marie L Vangu, who told me not to follow his way, but to become a doctor to heal others.

To my mother, Jeanne M Mboyo, who spared no penny to make my father's dream come true.

SUMMARY

The attention recently gained by functional brain imaging research in affective disorders is considerable. Decreases in regional cerebral blood flow in depressed patients have been reported in the limbic and paralimbic areas by tomographic imaging techniques (Ito et al, 1996; Mayberg et al, 1994). Studies examining the long term effects of electroconvulsive therapy (ECT) on the cerebral perfusion demonstrate contrasting results in both the responders and non responders (Silfverskiold et al, 1986; Nobler et al, 1994).

The aim ofthis study was to observe regional cerebral blood flow (rCBF) changes in patients with major depression while using brain SPECT imaging before and after a course of ECT.

15 patients with major depression diagnosed according to DSM-IV criteria were investigated in this study. They were 11 females and 4 males who did not respond to pharmaceutical treatment. Their mean age was 36.9 ± 11.9 and except for two who refused ECT after the pretreatment imaging, all the others scored at least 17 on the Hamilton Rating Scale for Depression (HAM-D), mean 25.8 ± 4.7.

The data analysis consisted of visual assessment and semiquantitative evaluation of ^{99m}Tc-HMPAO uptake ratios measured between cerebral regions of interest and the cerebellum.

The results in the group of responders showed obvious improvement on visual assessment and unchanged patterns in non responders. Two of the 15 patients showed signs of post traumatic stress disorder (PTSD) after ECT and demonstrated peculiar patterns regarding their response to therapy. When patients were considered as a whole, significant changes on the semiquantitative evaluation were noted in the anterior cingulate gyrus and the left frontal area, in keeping with available literature. When patients were separated in groups of responders versus non responders however, no significant change was noted between the pre and post ECT studies.

From the results it can be concluded that :

1. Findings in depression are "state" related and can be reversed by successful treatment.
2. Future studies need to find an explaination for the discrepancy between the visual and the semiquantitative method.
3. ^{99m}Tc-HMPAO SPECT may not be a good therapy monitor in depressed patients who later manifest symptomatology of PTSD.

ACKNOWLEDGEMENTS

I wish to thank the following:

- My wife Chantal and my two daughters, Mercy and Jolyne for all the support and the joy they fill me with

- Professor M Berk for accepting to supervise this thesis

- Professor J Esser for his guidance throughout my training

- Dr B van Heerden who helped me and who stimulated my interest in Brain Studies

- Professor M Mann for his academic and scientific support

- Mr I Boyd for sharing his precious time to analyse data for this study

- The staff of Tara H Moross Centre (Wards 6 and 7) and Johannesburg Hospital [Areas 487 (Psychiatry) and 559(Nuclear Medicine)] for the selection of patients and willingness to contribute to the success of this study. My special thanks in this matter are directed towards Dr U Subramaney, Sr N Morare and Mr D Maleeme

- To Ilze and Bronwen for typing this work to make it presentable

- Finally, God who made everything possible

TABLE OF CONTENTS

page

Declaration..... I

Dedication..... ii

Summary..... iii

Acknowledgements..... v

List of Abbreviations..... xi

CHAPTER 1: DEPRESSION..... 1

1.1 NEUROANATOMY OF DEPRESSION..... 2

1.2 PSYCHOPATHOLOGY AND CLINICAL PRESENTATION..... 5

1.2.1 PSYCHOPATHOLOGY..... 5

1.2.1.1 Mood disturbances..... 7

1.2.1.1.1. Depressed mood..... 7

1.2.1.1.2. Anhedonia and loss of interest..... 9

1.2.1.2 Psychomotor disturbances..... 10

1.2.1.3 Cognitive disturbances..... 10

1.2.1.4 Vegetative disturbances..... 11

1.2.2 DIAGNOSIS AND CLINICAL SUBTYPES..... 13

1.2.2.1 Depressive disorders..... 13

1.2.2.1.1 Major depressive disorders..... 13

1.2.2.1.2 Depressive disorders not otherwise specified..... 13

1.2.2.1.3 Dysthymic disorder..... 14

1.2.2.2 Bipolar disorders..... 15
1.2.2.2.1 Bipolar I disorder..... 15
1.2.2.2.2 Cyclothymic disorder..... 15
1.2.2.2.3 Bipolar II disorder..... 16
1.2.2.2.4 Mood disorder not otherwise specified..... 16

CHAPTER 2: ELECTROCONVULSIVE THERAPY..... 17

2.1 DEFINITION..... 18

2.2 HISTORY..... 18

2.3 EFFECTS OF ECT..... 18

2.3.1 Electroencephalogram..... 18
2.3.2 Cerebral blood flow..... 19

2.4 TREATMENT..... 19

2.4.1 Mechanism of action..... 19
2.4.2 Course..... 19
2.4.3 Resistance..... 21
2.4.4 Maintenance..... 21

2.5 INDICATIONS..... 21

2.6 COMPLICATIONS..... 21

2.6.1 Cardiovascular effects 22
2.6.2 Memory loss 22
2.6.2.1 Anterograde Amnesia 22
2.6.2.2 Retrograde Amnesia 23
2.6.2.3 Autobiographic Amnesia 23

2.7 CONTRA-INDICATIONS 23

2.7.1 Space occupying lesion 23
2.7.2 High intracranial pressure 24
2.7.3 Intracranial bleeding 24
2.7.4 Recent myocardial infarction 24

2.8 ECT AND DEPRESSION 24

CHAPTER 3: 99m Tc-HMPAO 27

3.1 INDICATIONS 28

3.1.1 Regional cerebral blood flow scintigraphy 28
3.1.2 In vitro leucocyte labelling 28

3.2 CONTRA-INDICATIONS 28

3.3 SIDE-EFFECTS 28

3.4 PHARMACO-KINETICS 29

3.5 DOSAGE 29

3.6 RADIATION DOSE 29

3.7 ADVANTAGES AND DISADVANTAGES 30

3.7.1 Advantages 30
3.7.2 Disadvantages 30

CHAPTER 4: SPECT 32

4.1 INTRODUCTION 33

4.2 CLINICAL APPLICATIONS 33

4.2.1 Brain SPECT Imaging with ^{99m}Tc-HMPAO 34

4.2.1.1 Normal Patterns 34
4.2.1.2 Abnormal Patterns 34

CHAPTER 5: METHODS 38

5.1 PATIENTS 39

5.2 PROCEDURE 42

5.2.1 Administration of ECT 42
5.2.2 Scan Acquisition and Image Processing 42

5.3 DATA ANALYSIS 45

5.3.1 Visual Assessment 45
5.3.2 Semiquantitative Analysis 45

CHAPTER 6: RESULTS 47

6.1 CLINICAL CHARACTERISTICS 48

6.2 SPECT RESULTS 48

6.2.1 Visual Assessment 48

6.2.2 Semiquantitative Results 51

CHAPTER 7: DISCUSSION 69

7.1 PATIENTS 70

7.2 MATERIALS AND METHODS 70

7.2.1 ECT Administration 70

7.2.2 Scan acquisition and Imaging processing 72

7.3 DATA ANALYSIS 72

7.4 RESULTS 74

CHAPTER 8: CONCLUSION 78

REFERENCES 80

APPENDIX 87

LIST OF ABBREVIATIONS

CT	=	Computed Tomography
MRI	=	Magnetic Resonance Imaging
PET	=	Positron Emission Tomography
SPECT	=	Single Photon Emission Computed Tomography
BGD	=	Basal Ganglia Disorders
VTA	=	Ventral Tegmental Area
DSM-III	=	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R	=	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	=	Electroconvulsive therapy
EEG	=	Electroencephalogram
SOL	=	Space Occupying Lesion
HDRS	=	Hamilton Depression Rating Scale
BH4	=	Tetrahydrobiopterin
HMPAO	=	Hexamethylpropyleneamine oxine
Tc	=	Technetium
IMP	=	Iodoamphetamine
I	=	Iodine
rCBF	=	Regional Cerebral Blood Flow
MBq	=	MegaBequerel
LOD	=	Late Onset Depression
PSE	=	Present State Examination
PTSD	=	Post Traumatic Stress Disorder
OML	=	Orbito-meatal Line
ROIs	=	Regions of Interest
AD	=	Alzheimer Disease

Chapter 1:

DEPRESSION

1.1 NEUROANATOMY OF DEPRESSION

With advanced imaging techniques, a living and working brain can be directly examined during episodes of clinical depression. This provides methods for investigating the suggestion that depression involves abnormal function in specific regions of the brain. The subregions implicated as abnormal in clinical depression comprise the frontal and temporal lobes, the basal ganglia, cerebellum and parts of the limbic system, usually the amygdala and anterior cingulate (George, 1994). Much of the groundwork of neuroanatomy of depression comes from studies using diverse structural as well as functional approaches, such as images taken at rest or following pharmacological and psychological activation; studies in primary and secondary depression, and also those studies correlating regional brain changes during depression with the eventual response to various treatments. At present, exquisite images of the structure of the brain can be provided with Computer Tomography (CT) Scans and Conventional Magnetic Resonance Imaging (MRI).

When dealing with depressed subjects, the imaging techniques become helpful in excluding other disease processes capable of causing depression such as stroke or multiple sclerosis. Formal research in primary depressed subjects has found subtle differences in the brain structure of depressed subjects compared to controls (Ketter et al, 1994).

In opposition to Structural Imaging Techniques (CT and MRI), brain function both at rest and during activation can be imaged with tools such as positron emission tomography (PET) and single photon emission tomography (SPECT). At the National Institute of Mental Health, Maryland, USA; a working neuroanatomical hypothesis-driven model is that the anterior limbic structures, amygdala, cingulate, and mesio-prefrontal cortex, show differential activity with normal emotions and differential dysfunction in mood disorders. The second hypothesis is that limbic dysfunction mood disorders reflects in interindividual clinical heterogeneity as well as intra individual mood state changes (Ketter, 1994).

The classic view of the limbic system is of a circle of a "limbus" on the medial aspect of both hemispheres that involves the amygdala and extends to the insula, the orbitofrontal cortex, and the anterior temporal lobes (Aggleton and Mishkin ; Papez, 1937).

The abovementioned anatomy is consistent with a mood processing system that can gather higher order sensory data, integrate it with past experience, and endow it with emotional significance yielding behavioural and hormonal responses. Generally, most functional and structural studies which showed abnormal patterns in patients with mood disorders did implicate limbic or paralimbic regions. Several studies in mood disorder subjects showed diffuse structural brain atrophy, increased ventricular size; or increased ventricle-to-brain ratios (VBR) compared to controls (Kellner, Rubinow, and Post). Others reported decreased size of the frontal or temporal regions in mood disorders such as bipolar type I or late onset depression (Altshuler et al, 1991). There are also studies which have reported an increased number of white matter hyperintensities in mood disorder subjects, particularly in those who have their first episode of depression late in life (Coffey et al, 1993). Evidence of decreases in cerebral activity in the prefrontal cortex associated with depression is found in most studies of primary depression using PET and SPECT (Baxter et al, 1989). Furthermore, work in the laboratory at the National Institute of Mental Health, USA, demonstrates that patients with mood disorders have statistically significant decrease in prefrontal blood flow compared with controls. Baxter and colleagues found relative hypofrontality in depressions of various etiologies including unipolar, bipolar and obsessive-compulsive disorders with depression (1989).

Negative correlation between depression scores and prefrontal activity has been found. That is, as subjects are more depressed , they have less activity in their prefrontal cortex, particularly on the left. In other words, the higher the Hamilton depression score, or the more depressed people are, the lower the brain activity in the dorsolateral or mesial prefrontal cortex (Ketter et al, 1994).

In depressed patients with impaired cognition, Dolan and colleagues (1993) have found that worsening cognitive dysfunction was related to decreases in the activity, primarily in the mesio-prefrontal cortex. Bench and co-workers also detected correlations between worsening psychomotor retardation and decreased activity in the left dorsolateral prefrontal cortex (Bench et al, 1992). Their study raises questions about the specificity of the changes seen on functional images, and whether the differences in normal controls are causally linked to depression, or are mere reflections of pathological behaviour, such as slowed thinking or psychomotor retardation.

Considering the localization theory in secondary depression, Basal ganglia disorders (BGD) provide a unique opportunity to study the regional neuroanatomy of depression, as pathological changes are confined to specific anatomical and neurochemical systems (Starkstein and Robinson, 1993 ; Mayeux, 1983). In pathologies such as Parkinson's disease, Huntington's disease and strokes involving the basal ganglia, depression occurs with mean frequency of about 40% (Mayberg, 1994). An advantage of using Basal ganglia disorders to study depression is the overlap of clinical signs and symptoms between these patients and those with primary affective disorders. Motor and cognitive slowing is observed in both bipolar disorder and in certain BGD, even when depressive symptoms are absent (Rogers et al, 1987).

In a comparison of depressed and non-depressed Parkinson's patients, selective hypometabolism involving the caudate, orbito frontal and inferior prefrontal cortex was noted in the group of depressed patients (Mayberg et al, 1990). In addition, frontal metabolism was inversely correlated with the magnitude of depressive symptoms as measured by the Hamilton Depression Rating Scale, a finding repeatedly observed in patients with primary depression. Although explicit mechanisms responsible for the frontal metabolic changes are unknown, hypotheses based on the known neurochemical and degenerative defects present in Parkinson's disease can be offered to account for the selective regional

abnormalities. Evidence from primate, rodent and human studies demonstrates that ascending dopaminergic projections from the ventral tegmental area (VTA) show regional specificity for the orbitofrontal cortex (Mayberg, 1994). Nonetheless, non-imaging studies could be used to further test hypotheses that primary degeneration of meso-cortico-limbic dopamine neurons in the VTA may lead to dysfunction of the orbitofrontal cortex, which secondarily affects serotinergic cell bodies in the dorsal raphe.

In summary, when Parkinson's disease, Huntington's disease, and stroke patients were compared, paralimbic frontal and temporal cortex hypometabolism differentiated the depressed from the non-depressed patients independent of disease etiology. Thus, the recognition of paralimbic cortical changes in depressed patients has potential clinical applications.

1.2 PSYCHOPATHOLOGY AND CLINICAL PRESENTATION

1.2.1 PSYCHOPATHOLOGY

Depressive syndrome like other illnesses, clusters into signs and symptoms that constitute major depressive episodes as termed by the Diagnostic and Statistical manual of Mental Disorders, ed 4 (DSM-IV).
The criteria selected by DSM-IV attempt to set an operational threshold for depressive disorders based on a specified number of items and their temporal patterns. These criteria are seen in Table I.

The DSM-IV criteria (Table II and III) provide only a general guide. For a definitive diagnosis of major depressive disorders, disturbances in mood, psychomotor activity, cognitive and vegetative spheres should be ordinarily present.

Table I

Criteria of Major Depressive Episode

A	Five (or more) of the following symptoms have been present during the same two week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly due to general medical condition, or mood-incongruent delusions or hallucinations. 1. Depressed mood most of the day, nearly everyday, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood. 2. Markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation made by others). 3. Significant weight loss when not dieting or weight gain (e.g. a change of more that 5% of body weight in a month) or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains. 4. Insomnia or hypersomnia nearly everyday. 5. Psychomotor agitation or retardation nearly everyday (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly everyday (not merely self reproach or guilt about being sick). 8. Diminished ability to think or concentrate, on indecisiveness nearly everyday (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide).
B	The symptoms do not meet criteria for a mixed episode.
C	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D	The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism)
E	The symptoms are not better accounted for by bereavement like after the loss of a loved one, the symptoms persist for longer than two months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
	Table from DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, ed 4.

1.2.1.1 Mood Disturbances

Usually considered the sine qua non of depression, mood change becomes manifest in a variety of disturbances, such as painful arousal, hypersensitivity or insensitivity to unpleasant events, insensitivity to pleasant events, reduced anticipatory pleasure, anhedonia or reduced consummatory pleasure, affective blunting, and apathy. In disturbances of mood, defining, describing, understanding and categorising feelings has long been among the most important tasks in psychiatry and, simultaneously, among the most difficult. Even to define such basic terms as "mood", "affect", "emotion", and "feelings"is difficult. The most common convention defines mood as a sustained or prevailing feeling tone or range of tones experienced by a person. Moods can be described by a number of important qualities: intensity (shallow or deep), range (broad or narrow or flat), stability (rigid to labile), reactivity to external events (none to much), periodicity (periodic to aperiodic), congruence with thought content (congruent or appropriate to incongruent), speed of resolution (rapid to slow), and viscosity (evanescent to persistent). Moods also serve as internal and external systems to elicit necessary help and support from the environment.

The two mood disturbances which are given selective weight in DSM-IV are:

1. Painfully arousal mood (depression)
2. Diminished capacity for pleasure (anhedonia)

1.2.1.1.1 Depressed Mood

This term refers to negative affective arousal, variously described as depressed, anguished, mournful, irritable, or anxious. These terms tend to banalize a morbidly painful emotion that is typically experienced as worse than any physical pain. There is a physical quality to depressed mood, which in the extreme is indescribably painful. Even when not so severe, depressive suffering is

qualitatively distinct from its neurotic counterparts, taking the form of groundless apprehensions with severe inner turmoil and torment. A depressed mood is common and appropriate after a disappointment or a loss. Alternative coping options and supportive social networks help many alleviate these brief depressive states and prevent most people from becoming chronically depressed. Nevertheless, people suffering from a chronic depressed mood, tend to view the world as a difficult place filled with obstacles and burdens, see themselves as victimized, and lack hope for the future.

Table II

Diagnostic Criteria for Major Depressive Disorder, Single Episode

A	Presence of a single major depressive episode.
B	The major depressive episode is not better accounted for by schizo-affective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
C	There has never been a manic episode, a mixed episode, or a hypomanic-like, mixed-like, or hypo manic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.
	Specify (for current or most recent episode): Severity / psychotic / remission specifiers Chronic With catatonic features With melancholic features With atypical features With post-partum onset
	Table from DSM-IV, Diagnostic and Statistical Manual of Mental Disorders ed 4.

Table III

Diagnostic Criteria for Major Depressive Disorder, Recurrent

A	Presence of two or more major depressive episodes. Note: To be considered separate episodes, there must be an interval of at least two consecutive months in which criteria are not met for a major depressive episode.
B	The major depressive episodes are not better accounted for by schizo-affective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
C	There has never been a manic episode, a mixed episode, or a hypomanic episode. **Note:** this exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.
	Specify (for current or most recent episode): Severity / psychotic / remission specifiers **Specify:** Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern
	Table from DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, ed 4.

1.2.1.1.2 Anhedonia and loss of interest

Paradoxically, in many persons with depressive disorder, the perception of pain is accompanied by an inability to experience normal emotions. These patients may lose the capacity to cry, a deficit that is reversed as the depression is lifting. In contrast to the schizophrenic patient's flat affect, the depressed patient suffers immensely from the inability to experience emotions.

1.2.1.2 Psychomotor disturbances

The most readily observed abnormality is agitation which manifests as pressured speech, restlessness, wringing of hands or pulling of hair. Agitation appears less specific to the disease than does retardation (slowing of psychomotor activity). Psychomotor retardation is believed to be the core or primary pathology in mood disorders. The morbid depression, described by the patients as being down, can be understood in terms of extreme psychomotor slowing. The patient feels inert and becomes unable to act physically and mentally. The subjective sense of slowing is a most pervasive and disabling aspect for the patient. The psychological dimension of retardation is most reliably elicited from depressed persons by interviewers with good verbal skills. Psychomotor slowing can be so extreme in young persons that they slide into a stupor, making them unable to participate even in such basic biological functions as feeding themselves. The latter often represents the precursor of bipolar disorder, which will declare itself by mania.

1.2.1.3 Cognitive disturbance

Negative self-evaluations are end-points of understanding depressed mood and behaviour as well as disturbed psychomotor activity.

Clinical patterns manifest by:

1. Ideas of deprivation and loss
2. Low esteem and self-confidence
3. Self-reproach and pathological guilt
4. Helplessness, hopelessness and pessimism and
5. Recurrent thoughts of death and suicide

Mood congruent psychotic features

Negative thinking or delusions dominate the depressive disorder with psychotic features. The delusional thinking in depression is derived from humankind's basic insecurities such as health, financial status, moral worth and relationships to others. The severely depressed patients may have delusions of worthlessness and sinfulness, and persecution. Depending on the affected sphere, a severely depressed patient can experience delusions of infidelity, delusions of ill health or even a nihilistic delusion in which parts of bodies are missing. In more severe illness, delusions of calamity and destruction may lead the patient to kill his or her children to save them from moral or physical decay, before committing suicide. In a small group of patients, auditory and visual hallucinations may be present in such a way that patients can hear accusatory voices or see themselves in coffins or graveyards.

Mood-incongruent psychotic features

Because of negative thoughts, up to 15% of untreated or inadequately treated patients give up hope that they will ever recover and so kill themselves. The risk of suicide is less pronounced during acute severe depression. Suicidal ideation is commonly expressed indirectly, such as in a wish not to wake up.

1.2.1.4 Vegetative disturbances

The limbic-diencephalic dysfunction is implicated among the measurable alterations of biorhythms accompanying mood change in depressive disorder. In melancholia, a form of depression, biological concomitants include profound reduction in appetite, sleep, and sexual functioning. Other alterations such as worsening of mood and psychomotor performance are also seen .

Nonetheless, an atypical pattern of depression is noted in a smaller

subgroup of persons where a reversal of the vegetative and circardian functions is expressed by increases in appetite and sleep, and sometimes in sexual functioning along with an evening worsening of mood.

Anorexia and weight loss are among the most reliable indicators of depressive disorder. Anorexia might be secondary to blunted olfactory or taste sensations or a decreased enjoyment of food, or to a delusional belief of food poisoning. Inanition in elderly persons can lead to malnutrition and electrolyte disturbances. Severe loss of weight over the age of 40 and greater, should be investigated to rule out malignancy. Also, decreased activity and over-eating may result in weight gain presenting as a bulimic pattern in young women. However, all bulimia nervosa is not the result of a mood disorder.

A cardinal sign of depression , sleep disturbance, often manifests in insomnia as multiple early morning awakenings rather than difficulty in falling asleep. Alcohol drinking and sedative-hypnotic agents used in an attempt to overcome the problem will reduce the number of awakenings in the short term but ultimately will lead to an aggravation of the insomnia. They are not antidepressants and tend to prolong the depression because of a further decrease of stage 3 and stage 4 sleep.

Hypersomnia is often seen in young depressed persons in whom the affective nature goes unrecognized and their slothfulness and tendency to slumber may be accounted to laziness. Circadian dysregulation is mainly expressed as disruption in temperature regulation, cortisol rhythms and sleep rhythms. Seasonality is another biorhythmic factor in terms of accentuation or precipitation of depression.

Both depressed men and women can manifest a decreased sexual desire. However, an increased sexual drive of a compulsive nature may be seen among a small subgroup of persons with depressive disorder.

1.2.2 DIAGNOSIS AND CLINICAL SUBTYPES

The main demarcation in the clinical terrain is between bipolar and depressive (unipolar) disorders.

1.2.2.1 Depressive Disorders

This category includes major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified (NOS).

1. Major depressive disorder

The diagnosis requirements of major depressive disorder as specified in the DSM-IV comprise (1) dysphoric mood or decreased interest in usual activities and (2) at least four additional classic depressive signs and symptoms, (3) which must be sustained for at least two weeks, and (4) cannot be explained by a process known to cause depressive symptoms, such as normal bereavement or certain physical conditions commonly associated with depression.

2. Depressive disorder not otherwise specified

It includes disorders with depressive features different from the diagnostic criteria for major depressive disorder, dysthymic disorder, adjustment disorder with depressed mood or mixed anxiety and depressed mood.

Examples of depressive disorder no otherwise specified include:

1. Premenstrual dysphoric disorder: symptoms must be severe enough to markedly interfere with work, school, or usual activities

and be entirely absent for at least one week postmenses.

2. Minor depressive disorder: episodes of at least two weeks of depressive symptoms fewer than those required for major depressive disorder.
3. Recurrent brief depressive disorder: depressive episodes occurring at least once a month for 12 months from two to fourteen days but not associated with the menstrual cycle.
4. Postpsychotic depressive disorder of schizophrenia.
5. Situations in which the clinician is unable to determine whether a depressive disorder is primarily due to a general medical condition or substance induced.

3. Dysthymic disorder

Dysthymic disorder differs from depressive disorder by the fact that it is not a sequel to well-defined major depressive episodes. Characteristics such as (1) low grade chronicity for at least two years, (2) insidious onset with origin often in childhood or adolescence, and (3) persistent or intermittent course, form the core concept of dysthymic disorder. Dysthymic disorder is socially described as an ambulatory disorder compatible with relatively stable social functioning. Its course corresponds to an insidious onset of depression dating back to late childhood or the teens, preceding any superimposed major depressive episodes by years, or even decades. Patients with dysthymic disorder view themselves as belonging to an aristocracy of suffering in that they complain of having been depressed since birth or of feeling depressed all the time. Although its clinical picture overlaps with that of major depressive disorder, it differs from it in that the symptoms tend to outnumber the signs (more subjective than objective depression).

1.2.2.2 Bipolar disorders

Bipolar I (Manic-depressive) disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified compose the four bipolar disorders included in DSM-IV.

1. Bipolar I disorder

It begins typically in the teenage years with the first episode being manic, depressive, or mixed. One common mode of onset is mild retarded depression, or hypomania for a few weeks or months, which then switches into a manic episode.

Six ways to subcategorise Bipolar I patients have been given in DSM-IV as follows: single manic episode, most recent episode hypomanic, most recent episode depressed and most recent episode unspecified.

On the average, manic episodes predominate in youth and depressive episodes in the late years. Bipolar I disorder in children is not as rare as previously thought.

2. Cyclothymic disorder

Cyclothymic disorder is characterized by short cycles of subsyndromal depression and hypomania which begins insidiously before the age of 21. Interpersonal friction and episodic promiscuous behaviour leads to repeated marital failures or romantic breakups in patients with cyclotymic disorders. These patients are dilettantes: they show great promise in many areas, but are rarely able to bring their efforts to fruition. Their lives are often a string of improvident activities. They are easily attracted to a new location, a new job, a new love partner but soon lose interest and leave in dissatisfaction. Thus being geographically unstable,

and in an attempt at self treatment, up to 50% of such persons go into polysubstance abuse.

3. Bipolar II disorder

Bipolar II disorder is an intermediatory form of depression and hypomanic episodes, differently expressed between the extremes of classic manic-depressive illness, and defined by at least one acute manic episode (Bipolar I disorder) and strictly defined major depressive disorder without any personal or familial history of mania. Bipolar II disorder may actually be more common than bipolar I disorder as noted in the outpatient setting, where as many as 30% of persons with major depressive disorder might conform to the bipolar II pattern. The hypomania at the end of depressive episodes in most bipolar II disorders does not persist long. Major depressive disorder superimposed on cyclothymic disorder, with hypomania preceding and following major depression is a common form of bipolar II disorder.

4. Mood disorder not otherwise specified

The DSM-IV diagnostic criteria defines this entity as being a category which includes disorders with mood symptoms that do not meet the criteria for any specific mood disorder and in which it is difficult to choose between depressive disorder not otherwise specified and bipolar disorder not otherwise specified such as an acute agitation (Kaplan, Benjamin, and Sadock, 1995).

Chapter 2:

ELECTRO CONVULSIVE THERAPY

ELECTRO CONVULSIVE THERAPY

2.1 DEFINITION

Electroconvulsive Therapy (ECT) is a procedure using an electrical current through the brain in order to induce generalised seizures lasting 25 to 150 seconds.

2.2 HISTORY

ECTs first modern application occurred in January 1934 by Ladislas J von Meduna whilst treating schizophrenia. Two percent incidence of fractures of the extremities, 17% incidence of dislocations, and 50% incidence of fractures of the spine, were initially associated with this procedure, until A E Bennet introduced the use of muscle relaxants to the procedure in 1940.

The first patient ever to receive ECT was found wandering around in a disorganised state, alternating between muteness and incoherent gibberish. Speaking his first coherent words, he said: "Not another! It will kill me!" however, he received 11 ECT treatments and fully recovered. When asked what had been happening to him, he replied: "I do not know, perhaps I have been asleep" (Kaplan, Benjamin, and Sadock, 1995). At present, mood disorders are the primary indications for ECT.

2.3 EFFECTS OF ECT

2.3.1 ELECTROENCEPHALOGRAM

A generalized central seizure produced by the ECT spreads through the cortex and ends with a period of electrical silence (postictal suppression) lasting up to 90 seconds. Twenty to thirty minutes after the postictal suppression there is a return to the preseizure electroencephalogram (EEG) pattern. The EEG returns to normal 1 to 12 months after treatment ends.

2.3.2 CEREBRAL BLOOD FLOW

Increases in cerebral blood flow, permeability of the blood-brain barrier, metabolic rate, and the consumption of oxygen and glucose in the neocortex and the hippocampus are noted during seizures. There is a global decrease in cerebral blood flow, especially in the frontal cortex in the postictal period. The latter may be more pronounced in responders that in non-responders.

2.4 TREATMENT

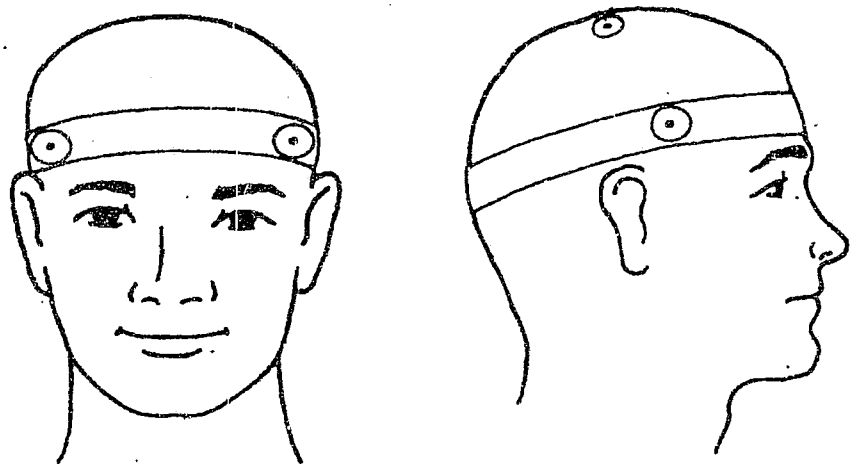
2.4.1 MECHANISM OF ACTION

Although there are clinical and physiological differences, some of the biological actions of ECT are similar to those of anti-depressant medications. In depression, for ECT to be effective, a seizure must occur. To have a therapeutic effect, the stimulus that produces seizures, must be sufficiently above the seizure threshold, especially for unilateral ECT (Fig. 1). In bilateral ECT the electrodes are placed on both frontotemporal regions whereas they are usually placed on the right side of the head in unilateral ECT.

2.4.2 COURSE

ECT is administered two to three times a week. Less cumulative memory loss is noted in the twice weekly schedule than in the thrice weekly schedule. The average course of ECT for melancholia is 6 to 12 treatments, but some patients require as many as 20. In mania, 8 to 20 ECT treatments are reported to be effective and 17 or more treatments in schizophrenia. One to four treatments should give a good response in catatonia, delusion, and psychogenic confusional states. ECT is generally discontinued in patients who have not responded with at least some bilateral administration (Fig. 1).

ELECTROCONVULSIVE THERAPY



Bilateral **Unilateral**

Fig 1: Type of electrode placement used with ECT - bilateral (left) and right unilateral nondominant (right).

2.4.3 RESISTANCE

Similar to inadequate drug dosages, insufficient stimulus dosage may contribute to resistance to ECT. Some patients start responding only after 10 to 15 bilateral treatments and require a total of 16 to 24 treatments for a complete response.

2.4.4 MAINTENANCE

For patients not tolerating or responding to continuation medications or who prefer ECT, continuation ECT is indicated. This type of treatment is administered at weekly intervals with its frequency decreasing gradually to once a month. When ECT is continued more than six months after remission, it is called maintenance ECT.

2.5 INDICATIONS

ECT is mainly used in depression, mania and schizophrenia. However, it can be used in a variety of conditions such as

- catatonia
- cycloid psychoses
- atypical psychoses
- delirium
- Parkinson's disease and
- epilepsy with alternating psychosis

2.6 COMPLICATIONS

The mortality rate with ECT is about 0,002 percent per treatment (Kaplan, Benjamin, and Sadock, 1995). Cardiovascular complications are responsible for two thirds of deaths occurring immediately after ECT.

2.6.1 CARDIOVASCULAR SIDE EFFECTS

ECT is associated with transient systemic hypertension produced by stimulation of the sympathetic nervous system. Bradyarrhythmias, Tachyarrhythmias, and T wave changes can be precipitated by vagal and sympathetic effects.

In a study by Zielinski et al (1993) to determine the safety of ECT for depressed patients with serious cardiac disease, the rate of complications in patients with major depressive disorder and left ventricular impairment, ventricular arrthymias, and / or conduction delay was compared to the rate of complications in a matched comparison group of depressed patients without cardiac disease after ECT. The results show a significantly higher rate of cardiac complications during ECT in patients with cardiac disease. However, close monitoring for the development of asthma and ischaemic episodes may help to safely give ECT in patients with severe cardiac disease.

2.6.2 MEMORY LOSS

Memory problems associated with ECT are confounded by the frequent finding of memory deficits in depression. When depression appears to be associated with impairment of the acquisition of new information, ECT causes transient disruption of the retention of new information, with no change in acquisition or with increased acquisition. Memory problems are most common with bilateral ECT. Furthermore, as many as 75% of patients receiving ECT say that memory loss is the worst side effect (Kaplan, Benjamin, and Sadock, 1995).

2.6.2.1 Anterograde Amnesia

This is the impairment of the ability to recall events following ECT and is presented maximally within 45 minutes after each ECT treatment, returning to

normal in an average of 72 days after ECT ends, but always within six months for both bilateral and unilateral ECT.

2.6.2.2 Retrograde Amnesia

This loss of memory for information learned before ECT shows a temporal gradient, with information acquired closest to the treatment being most affected. Loss of memory for events occurring a few days before ECT is most common and is persistent. But memories for events occurring one to two years before ECT may also be lost permanently.

2.6.2.3 Autobiographic Amnesia

The recall of personal events or autobiographic events reported by patients before ECT may not be remembered six to seven months after completion of ECT. The events more likely to be permanently forgotten are those that occurred shortly before ECT, such as those associated with hospital admission than the events in the distant past.

2.7 CONTRA-INDICATIONS

Conditions associated with substantial risk as listed below constitute ECT contra-indications.

2.7.1 Space-occupying lesion (SOL)

The increased cerebral blood flow and permeability of the blood-brain barrier to water constitute the major risk of ECT to patients with SOL. They can produce excessive edema around the lesion and lead to herniation.

2.7.2 High intra cranial pressure

ECT may increase the pre-existing intra cranial pressure.

2.7.3 Intra cranial bleeding

Patients with unstable aneurysms or vascular malformations are at risk of rebleeding.

2.7.4 Recent myocardial infarctions

There is risk of reinfarction if the cardiac function is unstable. Heart failure, ventricular arrhythmia and cardiac rupture may occur.

2.8 ECT AND DEPRESSION

Being the primary indication of ECT, depression has been studied considering response to ECT, the biological evidence of its recovery after ECT, its assessment in medication combined with ECT and so forth.

The prediction of treatment response is a continual concern for psychiatrists and their patients (Scott et al, 1994) attempted to identify depressed patients for whom ECT would be an effective treatment. He used many biological and physiological measures such as monoamines and metabolites, calcium, cortisol, dexamethasone suppression test, thyrotrophin-releasing hormone (TRH), release of anterior and posterior pituitary hormones, electroencephalogram, seizure threshold and seizure activity, and autonomic changes.

The findings of the study showed that most contemporary depressed patients will do well in the short term post-ECT but little or no benefit was gained from ECT by a small yet significant minority. Furthermore, depressed patients showed a wide range of physiological responses to ECT. None of the biological

measures were shown to be superior to clinical predictors.

In a similar study, twenty-six patients with major depression were selected using the DSM-III-R criteria. Patients with a history of drug or alcohol abuse and those pregnant were excluded. Routine examination and investigation of haematology, biochemistry, thyroid function, urine analysis and chest radiography were used to exclude patients with significant systemic illnesses. The Hamilton Depression Rating Scale (HDRS) was used throughout and the score of greater than 17 before ECT was required. A score of less than 7 was defined as response to ECT. The estimation of phenylalanine and tyrosine was performed on the basis that tetrahydrobiopterin (BH4), the predominant biopterin in human tissue and fluids, is the essential cofactor for the hydroxylation of tyrosine and tryptophan. The serum level of BH4 was found to be reduced before ECT and returned to normal after ECT. This finding could support the mechanism of noradrenaline and serotonin deficiencies in depression (Levitt et al, 1965).

Relapse rates post-ECT being a problem in depression, some trials examined whether concomitant therapy with antidepressant medication would reduce the number of ECT treatments needed. It is known that relapse rates may approach 50% if no antidepressant treatment is instituted in the first few months following symptomatic remission of episodes of major depression (Mindham, Howland, and Shephred, 1973 ; Prien, Klett, and Coffey, 1973). While relapse rates are sharply reduced by continuing antidepressant treatment following clinical response, untreated patients following remission of depression with electroconvulsive therapy manifest high rates of early relapse (Imlah et al, 1965).

Therapy continuation with antidepressant medications is believed to reduce relapse rates from approximately 50% to 20% in the first few months following response to ECT. In a study by Harold et al (1990) on the impact of medication resistance and continuation Pharmacotherapy on relapse following response to ECT in major depression, fifty to eighty patients were monitored until relapse, or

for one year following clinical response to ECT. The rate of relapse was found to be substantially higher in patients who had failed adequate antidepressant medication trial prior to ECT than in non-resistant patients.

Chapter 3:

TECHNETIUM-HMPAO

TECHNETIUM-HMPAO (Hexamethylpropylene amine oxine)

HMPAO is a derivative of propyleneamine oxime (PAO) which has high retention in the brain to permit tomographic imaging. It has a fairly high first pass extraction through the cerebral circulation and when complexed to technetium, it does not appear to redistribute within the brain for up to 8 hours after being injected (Sharp et al, 1986).

3.1 INDICATIONS

3.1.1 Regional cerebral blood flow scintigraphy

^{99m}Tc-HMPAO intravenous injection is used for regional cerebral flow scintigraphy. It has been used in stroke, epilepsy, dementia mainly of Alzheimer's type, transient ischaemic attack, migraine, tumours of the brain, schizophrenia and depression.

3.1.2 In vitro leucocyte labelling

^{99m}Tc-HMPAO labelled leucocytes may help to detect the site of local infection, in the investigation of the pyrexia of unknown origin (PUO) and in the evaluation of inflammatory bowel disease.

3.2 CONTRA-INDICATIONS

No specific contra-indications are known.

3.3 SIDE-EFFECTS

Two cases of mild hypersensitivity expressed as an urticarial erythematous rash have been reported following direct intravenous injection of the reconstituted product (Amersham package insert).

3.4 PHARMACO-KINETICS

As regional cerebral flow agent, ^{99m}Tc-HMPAO is rapidly cleared from the blood after intravenous injection. Maximum brain uptake is about 3,5 - 7% of the injected dose within one minute of injection. Up to 15% of the cerebral activity washes out of the brain by two minutes post-injection. Thereafter little loss of activity in the following 24 hours is noted except by physical decay of Technetium. Non-associated brain activity is widely distributed throughout the body particularly in muscle and soft tissue. 30% of the injected dose is found in the liver and gastrointestinal tract immediately after injection, and about 50% is excreted through the gut over 48 hours. Kidney secretion is about 40% over the 48 hours after injection resulting in a reduction in general muscle and soft tissue background.

3.5 DOSAGE

In a normal adult (approximately 70kg) up to 740 MBQ (20mCi) can be given safely using the intravenous injection.

3.6 RADIATION DOSE

The absorbed radiation dose to humans after intravenous administration is estimated in Table IV. The maximum dose with 4 hours bladder voiding is 9.5 mGy but increases to 44.5 mGy with no bladder voiding.

3.7 ADVANTAGES AND DISADVANTAGES AS A BRAIN PERFUSION AGENT

3.7.1 Advantages

- On site preparation facilitating an in-hospital use
- No beta radiation resulting in a low total body radiation
- Lower cost as compared to other agents for functional brain imaging
- Ideal physical characteristics:
    - Short but reasonable half-life of six hours. This permits imaging within working hours, but a short exposure to radiation
    - High photon flux with good tissue penetration and easy collimation

3.7.2 Disadvantages

- Unstable in vitro by 30 minutes after preparation. Therefore, it imposes restriction on its clinical availability of certain circumstances.
- Variable radiochemical purity results on quality control.

Table IV

Organ	Absorbed dose per unit activity administered (mGy/MBQ) Adult
Adrenals	5.3E - 03
Bladder	2.3E - 02
Bone surfaces	5.1E - 03
Brain	6.8E - 03
Breast	2.0E - 03
Gall bladder	1.8E - 02
GI tract	
Stomach	6.4E - 03
SI	1.2E - 02
ULI	1.8E - 02
LLI	1.5E - 02
Heart	3.7E - 03
Kidneys	3.4E - 02
Liver	8.6E - 03
Lungs	1.1E - 02
Muscles	2.8E - 03
Oesophagus	2.6E - 03
Ovaries	6.6E - 03
Pancreas	5.1E - 03
Red marrow	3.4E - 03
Skin	1.6E - 03
Spleen	4.3E - 03
Testes	2.4E - 03
Thymus	2.6E - 03
Thyroid	2.6E - 02
Uterus	6.6E - 03
Remaining organs	3.2E - 03
Effective dose equivalent (mSv/MBQ)	**1.1E - 02**

Effective Dose us 4.7 mSv/500 MBQ (70 kg individual).

From Ceretec™ insert, American International PLC Amersham UK

Chapter 4:

SPECT

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

4.1 INTRODUCTION

SPECT is a technique for producing cross-sectional images of radiotracer distribution in the body. It is able to remove overlying structures capable of obscuring an abnormality, thereby improving the contrast.

Acquisition of data is usually performed over 180° or 360° in small angular steps. SPECT techniques provide a powerful window into the function of the brain and promise to become an important tool in the routine clinical evaluation of patients with neurological and psychiatric diseases. Some radio tracers that cross the blood-brain barrier, distribute proportionally to regional cerebral blood flow and remain fixed in the brain for a sufficiently long time to permit SPECT imaging (Murray and Ell, 1994).

4.2 CLINICAL APPLICATIONS

The main interest in SPECT at present is in brain imaging, to measure brain blood flow and metabolism.

In general, several radiopharmaceuticals can be used with brain SPECT, but three are well known and experienced worldwide.

The first, a labelled gas, Xenon^{133}, has been used for two-dimensional measures of cerebral flow and the second is an amphetamine labelled with Iodine^{123} (Iodoamphetamine), which has a higher energy and a longer half-life.

Hexamethylpropyleneamine oxine, a compound labelled with ^{99m}Tc,abreviated HMPAO, is the third radiopharmaceutical which can be given in larger doses that easily cross over from the blood to the brain, and imaging may begin as early as 15 minutes post-injection(Gottschalck, Hoffer, and Potchen, 1979).

Ethyl cystein dimer (ECD) with similar properties to HMPAO can be used for brain SPECT imaging.

4.2.1 BRAIN SPECT IMAGING WITH ^{99m}Tc-HMPAO

4.2.1.1 Normal Patterns

In a study by Catafau et al (1996) the normal pattern of regional cerebral blood flow distribution was semi- quantitatively measured using ^{99m}Tc-HMPAO in 40 normal young and 23 normal aged volunteers. The results show the cerebellum and the occipital lobe to be the most highly perfused regions whereas slightly lower perfusion ratios were noted in the remaining cortical regions (temporal, parietal, frontal and basal ganglia). When comparing young subjects to aged subjects, lower regional cerebral flow was noted in the left frontal and temporal lobes in the aged group, which the authors attributed to probable cerebral atrophy. This study was up to the time of this dissertation, the one with the largest number of "normal volunteers".

4.2.1.2 Abnormal Patterns

Kumar et al (1991) studied nine patients with history of late onset depression (LOD). He included patients with no history of a psychiatric disorder before the age of 60 and excluded those with a history of any other disease or event that could significantly affect cerebral structure or function except for well controlled mild hypertension. The average Hamilton Depression Rating Scale (HAM-D) score was 23 ± 3 before treatment. Five subjects were treated with ECT whereas the other five were treated medically with Nortriptyline. The outcome data indicate that SPECT may already be useful for differentiating depression with pseudo dementia from dementia with secondary depression.

To test the hypothesis that selective dysfunction of the paralimbic cortex such as orbital frontal, cingulate and anterior temporal cortex, is present in depressed patients, brain perfusion was measured in a homogenous group of refractory, familial, unipolar depressed patients using ^{99m}Tc-HMPAO SPECT at the

psychiatry service of the Johns Hopkins Hospital, Baltimore, USA. The study included 13 patients (men and women), aged 20 - 55 years, with severe unipolar depression confirmed by the Diagnostic and Statistical manual of Mental Disorders, Third edition - Revised (DSM-III-R) criteria and also by the present state examination (PSE) (Wing et al, 1974). From clinical histories, physical examinations or laboratory tests; patients were excluded if they had any suggestion of thyroid disease, stroke, head trauma, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease or other movement disorders, present or past manic or hypomanic episodes, obsessive compulsive disorder or psychiatric symptoms. Neuroleptic, vasodilator or dopamine-agonist medication, polysubstance abuse or electroconvulsive therapy within 6 months were also factors for exclusion from the study. Data analysis was performed using quantitative methods and the results demonstrated significant bilaterally decreased relative blood flow in the frontal cortex, anterior temporal cortex, anterior cingulate gyrus and caudate in the depressed patients compared with the non-depressed healthy controls. The paralimbic regions, specifically the inferior frontal and cingulate cortex, showed the greatest decreases in blood flow. The overall findings implicate selective dysfunction of paralimbic brain regions in clinically depressed patients, independent of their medication use, and support the concept of specific neural systems that regulate mood (Mayberg et al, 1994).

The uptake of ^{99m}Tc-HMPAO in depression has been also examined in different studies comparing the pre- and post-treatment findings as well as depression findings from other pathologies.

In a study by Goodwin et al (1993) twenty-eight patients with a major depressive episode were investigated at rest using SPECT with ^{99m}Tc-HMPAO and followed up for a period of 9 - 28 months after full recovery. They were all unipolar and rated with 17-Hamilton Scale. The ^{99m}Tc-HMPAO uptake relative to calcarine/occipital cortex was determined. The findings give potential focus to the neuropharmacological analysis of depressive illness as the topography of the

state change in brain function implicates dopamine function.

Using SPECT with a ^{99m}Tc-HMPAO perfusion technique, Thomas et al(1993) studied the regional cerebral blood flow (rCBF) of 42 drug free in-patients of a department of general psychiatry. Twenty-one were suffering from major depression and twenty-one from dysthymia with the super-imposed diagnosis of a major depressive episode. Significantly lower frontal rCBF ratios were noted in patients with major depression compared to the other group. However, no correlation between the severity of the illness and the rCBF was noted.

The uptake of ^{99m}Tc-HMPAO has also been investigated during the course of ECT or in the period before and after ECT. In a study case by Petrocca et al (1995) who treated a patient's major depression and cotard's syndrome (the delusion of being dead) with a complete resolution after twelve ECT treatments, SPECT study performed one week before ECT showed reduced blood flow in the frontoparietal medial and dorsolateral frontal cortex, basal ganglia, and thalamus whereas SPECT one month after ECT showed increased perfusion in the same afore mentioned regions.

This case of psychiatric improvement accompanied by increased blood flow in specific brain areas, suggests that cotard's syndrome in the context of major depression may be successfully treated with ECT.

Bojc et al (1989) studied perfusion changes using ^{99m}Tc-HMPAO during the acute phase of ECT. The study included eleven patients: eight with a DSM-III diagnosis of major depressive disorder and three with schizo affective disorder while those suffering from organic brain disease or alcoholism and those previously treated with ECT were excluded. Both visual assessment and the semi-quatitative measurement of the isotope uptake were used in baseline studies and studies during ECT. ECT was said to cause a redistribution of the tracer uptake in that the uptake became more pronounced in frontal parts of the brain and in the basal ganglia than in posterior parts of the cortex, and the thalamus in patients with major depression.

The last reviewed study is quite similar to our thesis subject. However,

differences are noted in patients' inclusion criteria, diagnosis criteria, scan acquisition, image processing and data analysis. In fact, twenty in-patients with major depression (15 women and 5 men aged 41 - 73 years) who had not responded to antidepressant medication were studied after meeting the DSM-III-R criteria for major depressive disorder (11 unipolar, 9 bipolar) and scored at least 18 on the HDM-D. The ^{99m}Tc-HMPAO brain SPECT uptake on these patients was performed 2 - 4 days before and 5 - 8 days after a course of ECT. Electrode placement was bilateral frontotemporal in all patients.

Patients on medication capable to affect SPECT evaluation and those with a history of neurological disorder, head trauma associated with loss of consciousness, suicide attempt, substance abuse or any current, severe medical condition were excluded from the study. Semiquatitative SPECT analysis was performed by applying preformed templates to transaxial SPECT slices, parallel to the orbitomeatal line (OML). The results demonstrated significantly increased ^{99m}Tc-HMPAO uptake in patients who responded to ECT but remained unchanged in patients who did not respond to the treatment (response defined as a reduction of at least 60% on the HMD-D). Using the spearmean correctional analysis between HAM-D scores and ^{99m}Tc-HMPAO uptake ratios, an inverse correlation was observed . The clinical improvement was positively correlated with the increase in tracer uptake. The most robust change was observed in the anterior cingulate gyrus, which is part of the paralimbic cortex. These findings signify that reduced rCBF in depression is a "state-related property and is reversible by successful treatment" (Bonne et al, 1996).

Chapter 5:

METHODS

5.1 PATIENTS

Fifteen in-patients with major depression who had not responded to antidepressant medication were included in the study. Out of these, eleven were females and four were males, with their ages ranging from 23yrs to 53yrs (mean age 36.9 + 11.9 yrs).

All these patients met the DSM-IV criteria for major depressive disorders (8 unipolar, 7 bipolar) and except for two, all had scores of at least 17 on the 17 items of the Hamilton Rating Scale for depression (HAM-D) [Hamilton, 1960]. See Tables IV and V. The two non-scored patients refused ECT on the day of first treatment but indeed had undergone pre-ECT scintigraphic imaging. No patient had undergone ECT in the six months before the study, and, except for Lithium, all antidepressant and antipsychotic medications were withdrawn during the ECT course.

Benzodiazepines were not given to patients, neither during ECT, nor in periods before SPECT imaging. None of the patients studied were taking somatic medication or had a history of neurological disorder, head injury, substance abuse or any psychiatric disease other than major depression.

The study was approved by the Human Ethics Committee of the University of the Wiwatersrand. Informed consent was obtained from all patients which explicitly explained the nature of the study. Only 15 patients responding to the Selection criteria (Table VI) could be selected from January 1997 to November 1997. Two patients did not have ECT (treatment refused).

Table IV

Patient No.	Sex	Clinical Staff
1	F	U
2	F	B
3	F	B
4	F	B
5	F	U
6	M	U
7	M	U
8	M	B
9	M	U
10	F	B
11	F	U
12	F	B
13	F	B
14*	F	U
15*	F	U

* Patients who refused ECT; U = Unipolar Depression; B = Bipolar Depression

Table V

Patient No.	Age	HAM-D Score (Pre-ECT)
1	28	29
2	54	23
3	53	34
4	44	26
5	25	25
6	51	21
7	31	17
8	25	22
9	24	32
10	47	28
11	23	31
12	26	22
13	39	25
14	50	....
15	33	....
Mean ± 5.d	36.9 ± 11.9	25.8 ± 4.7*

*Only patients scored were considered; .... No pre-ECT scores were available

Table VI

SELECTION CRITERIA	
1. INCLUSION	
- Under 60yrs of age	
- Major depressive disorder diagnosed clinically and enhanced by the 17- items on the HAM-D	
2. EXCLUSION	
- Previous neurological or psychiatric diseases	
- Previous head injury	-No severe medical illness
- Substance abuse	-No recent ECT (within the past six mounths)

5.2 Procedure

5.2.1 Administration of ECT

Electroconvulsive therapy was administered two to three times a week. Anaesthesia and muscle relaxants were induced by intravenous administration of etomidate (0.15 - 0.30 mg/kg body weight) or brietal sodium (1mg/kg body weight) and succinylcholine (0.5 - 1.0 mg/kg body weight). Electrode placement was bilateral fronto-temporal for all patients (Fig 1) and a brief pulsed, bidirectional, constant stimulus was administered using Thymatron devices. Seizures were monitored with two-channel electroencephalography. The ECT course was continued until a stable response had been achieved and for up to 12 treatments if the patient did not respond (mean 10.0 ± 2.3 [Range 6 - 14] treatments per patient), except for one patient (Table VII).

5.2.2 Scan Acquisition and Image Processing

SPECT imaging was performed 1 - 7 days (mean 2.6 ± 1.9) before the beginning of the ECT series and 3 - 11 days (mean 5.3 ± 2.3) after its termination (Table VII).

Table VII

Patient No.	Pre-ECT Imaging Day	No. of ECT	Post ECT Imaging Day
1	1	12	6
2	7	6	11
3	2	12	7
4	2	12	4
5	1	10	7
6	1	12	3
7	1	8	5
8	3	12	6
9	3	8	4
10	1	8	3
11	3	14*	3
12	6	8	3
13	3	8	3
Mean ± 5.d	2.6 ± 1.9	10.04 ± 2.3	5.3 ± 2.3

* More than 12 treatments

All subjects received an intravenous injection of 740 MBq of 99mTc-HMPAO through a previously placed drip in the cubital fossa. They were in a quiet and dimmed room with their eyes open and ears unplugged for approximately 30 minutes before the administration of the 99mTc-HMPAO injection. Image acquisition began 10 to 20 minutes after the injection of the radiotracer. Patients were placed in a supine position, with head immobilised on a head rest and secured with Velcro front and/or chin-straps.

SPECT images were obtained with a dual-head rotating gamma camera equipped with a low-energy, high-resolution collimators (Fig 2). Data was collected in 120 projections, on a step and shoot mode, through 180 degree rotation

per head using 128 x 128 matrix resolution. Processing included normalisation, back projection, filtering and attenuation correction. Using a preset program, reconstruction was carried out with a Metz 308 filter on a 64 x 64 matrix and a slice thickness of 1 pixel (0.44cm). Images were reconstructed in the transaxial oblique, sagittal, coronal, temporal-oblique and tempo-coronal slices. The first slice parallel to the orbito-meatal line (OML) and the last two slices parallel to the temporal plane. Another preset program was used to compare the reconstructed data of pre and post ECT by placing corresponding slices one above the other.

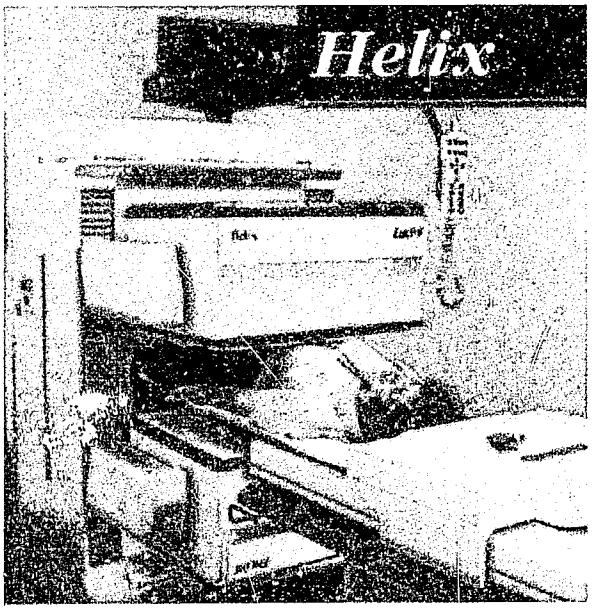


Fig 2: Dual-head multi-purpose Slip-Ring integrated digital gamma camera. Reproduced from a Handbook of Elscint Nuclear Imaging Procedures with permission.

5.3 DATA ANALYSIS

The raw data of our study were processed both by visual assessment and semiquantitative SPECT analysis.

5.3.1 VISUAL ASSESSMENT

The images obtained from the ^{99m}Tc-HMPAO Brain Scan before and after ECT were visually interpreted by a brain expert Nuclear physician and other Nuclear Physicians. The visual assessment was simply to look at cerebral and cerebellum perfusion and a specific attention was paid to perfusion abnormalities (diminished or absent perfusion) in different anatomic location from the study before to the one after ECT.

5.3.2 SEMIQUANTITATIVE ANALYSIS

Semiquantitative SPECT analysis was performed by applying preformed templates to transaxial SPECT slices, parallel to the OML. Three templates were used to delineate anatomic structures at approximately 2.6, 4.6 and 5.6 cm above the OML in a method similar to study by Daniela et al (1988) and Bonne et al (1996). Regions of interest (ROIs) were defined on the templates (Fig 3). The position of the ROIs within the template were relative to the anatomic region of choice while the size of the ROIs was the same for all. The relative cerebral count was calculated using the total count per pixel for each ROI. This relative cerebral count was later divided by maximal cerebellum uptake to establish the CBF ratio for subsequent use of statistical comparison.

The data were analysed for whole cerebral count and separately for each hemisphere in the three transaxial brain slices. Because of the sample size and also not being sure if the ^{99m}Tc-HMPAO uptake values are normally distributed in our patient groups, nonparametric statistics were used to compare significance

levels.

Pretreatment 99mTc-HMPAO uptake values were compared between responders and nonresponders by means of Wilcoxon signed rank test and the same procedure was used to compare the pre-ECT versus post-ECT cerebral uptake in responders and nonresponders separately.

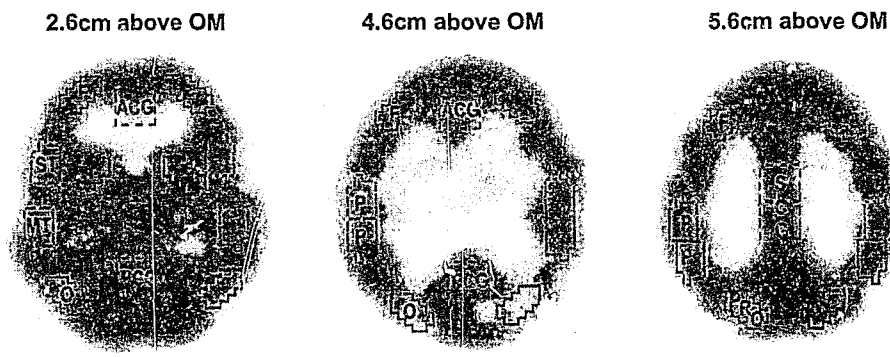


Fig 3: Regions of interest within the three templates. F = frontal lobe; ST = superior temporal lobe; MT = middle temporal lobe; O = occipital lobe; ACG = anterior cingulale gyrus; PCG = posterior cingulate gyrus; BG = basal ganglia; P = parietal lobe; PRO = Parieto-occipital cortex; SCG = superior gingulate gyrus.

Chapter 6:

RESULTS

6.1 CLINICAL CHARACTERISTICS

Seven of the thirteen patients responded to ECT with at least an 80% reduction in the pretreatment HAM-D score. Two patients had shown clinical features of post-trauma stress disorder and of these, one responded and the other did not. A significant difference between the responder and the nonresponder was noted in the post-treatment HAM-D scores ($p < 0.001$)

6.2 SPECT RESULTS

6.2.1 Visual Assessment

The regional cerebral blood flow is compared between baseline SPECT study and post-ECT study in a table which also gives the outcome of therapy as well as both pre and post HAM-D scores (Table VIII).

Two independents observers had 100% correlation in 14 of 15 patients. A group of reporting of a least two other observers had the same outcome.

Table VIII

Patient No.	ECT Results	Pre-HAM-D	Post-HAM-D	Baseline SPECT	Post-SPECT
1	Resp.	29	4	Hypo frontal L	→Improved
				Hypo temporal L+R	→Improved
				Abs. antero medial temporal L+R	→Improved R but very little improvement in L
				Hypo occipital L	→Improved
2	NResp.	23	14	Hypo frontal L+R (L>>>R)	→Unchanged
				Hypo ACG	→Unchanged
				Hypo temporal R	→Unchanged
				Hypo temporal L with abs. antero medial	→Little Improvement
3	Resp.	34	6	Hypo temporal R	→Improved
				Abs. anterior temporal L	→Improved
4	NResp.	26	23	Hypo postero lateral frontal R and antero medial frontal L	→Worsened
				Hypo temporal L	→Little Improvement in lateral part
				Hypo antero medial temporal R	→Unchanged
5	NResp.	25	29	Hypo temporal L antero medial temporal R	→Worsened
				Hypo BGs	→Improved
				Hypo ACG	→Unchanged
6	Resp.	21	2	Hypo frontal L	→Improved
				Hypo ACG	→Improved
				Hypo temporal L+R	→Improved
				Abs. antero medial temporal L	→Improved
				Hypo BGs	→Improved

7	NResp.	17	17	Hypo frontal L	→Unchanged
				Hypo BGs	→Improved
				Hypo temporal L	→Unchanged
					→Worsen frontal R
8	NResp.	22	18	Hypo frontal L+R	→Unchanged
				Hypo BGs	→Improved
				Hypo occipital L	→ ± Improved
9*	Resp.	32	6	Hypo temporal L	→Little Improvement
				Hypo frontal L	→Unchanged
				Hypo occipital R	→Unchanged
10	Resp.	28	5	Hypo frontal L	→Improved
				Hypo temporal L+R	→Improved
11*	NResp.	31	16	Hypo frontal L	→Worsened
				Hypo temporal R antero medially	→Worsened
					→Worsening of Frontal R
12	Resp.	22	3	Hypo frontal L+R	→Improved R
				Hypo temporal L	→Unchanged
				Hypo ACG	→Improved
				BG, R	→Improved temporal R
13	Resp.	25	3	Hypo frontal L+R	→Improved
				Abs. Temporal L	→Improved
14#				Hypo frontal R	
				Hypo temporal R	
				Hypo parietal L	
15#				Hypo temporal L+R	
				Hypo frontal L+R	

Resp. = Responder; NResp. = Nonresponder; ACG = Anterior cingulate gyrus; BGs = Basal Ganglia; Hypo = Hypoperfusion; L = Left; R = Right; Abs. = Absent;

*Patients in Post Traumatic Stress Disorder (PTSD) after treatment.

#Patients with pre-ECT imaging only.

The regional perfusion abnormalities noted in the above table can be summarised as follows for the pre-ECT studies:

1. Temporal regions abnormalities are seen in all 15 patients (100%) with left involvement in 13 patients (86,7%) vs right in 11 patients (73,3%).

2. Frontal regions abnormalities in 13 patients (86,7%) with left involvement in 12 patients (80%) vs right involvement in 7 patients (47%).

3. Left or right basal ganglia in 5 patients (33,3%) with right involvement in all 5 patients vs left in 4 patients (26,7%).

4. Anterior cingulate gyrus in 4 patients (26,7%) as a whole.

5. Occipital areas in 3 patients (20%) , left involvement in two patients and right involvement in one patient.

6. Left parietal area was involved in 1 patient (6,7%).

These results correlate with the study by Yazici et al (1992), in which ^{99m}Tc-HMPAO changes in rCBF were assessed in 14 patients with major depression. They found that rCBF seems to be decreased in the left frontal and in bilateral temporal regions.

They also correlate with the findings of Austin et al (1992) in a study where forty patients with a major depressive episode were imaged using SPECT with 99m Tc-HMPAO and a reduced uptake in the majority of cortical and subcortical regions examined was most significant in temporal and frontal areas.

When responders were compared with nonresponders, all responders, except for one showed improvement in the hypoperfused areas or regions of absent

perfusion.

The patient who did not show improvement had unchanged patterns and was diagnosed to be in PTSD in post ECT period.

One responder showed improvement of perfusion in right hemisphere only and her ECT was stopped as she became manic.

Two responders had occipital abnormal perfusion. One showed improvement but the other one showed unchanged pattern (PTSD in post ECT period).

All nonresponders showed unchanged to worsening cerebral perfusion, except for the BGs which improved in those three patients with baseline abnormal perfusion. One nonresponder had occipital abnormality of perfusion which showed some improvement.

The only parietal change was seen in a patient who refused ECT.
Only one nonresponder showed worsening of perfusion in all areas. She was diagnosed to be in PTSD in post-ECT.

6.2.2 Semiquantitative Results

Our results were derived from statistical manipulation of data from different ROIs at different levels above the OML, using the following:

1. Mean ($\bar{x}$):

$$\bar{x} = (x_1 + x_2 + \ldots\ldots\ldots\ldots + x_m) \,/\, m$$

2. Standard deviation of sample (SD):

$$SD = \sqrt{\frac{\sum (x_1 - \bar{x})^2}{N - 1}}$$

3. t -test:

$$t = \frac{\bar{x} \times \sqrt{N}}{SD}$$

4. P value based on t-test (Two-tailed)

5. Signed rank sum considering the critical values (Two-tailed) of Wilcoxon W.

The mean value of the difference was determined for each slice and its statistical significance was guaged by both parametric and non-parametric methods using the above mentioned formulae. The signed rank sum was obtained by ranking all the unsigned differences in the cerebellar ratios of a specified slice, assigning the sign of the difference to the rank and summing the signed ranks.
Tables IX to XVII give the statistical results of our study.

Table IX: Differences between pre- and post-treatment cerebellar ratios at OM + 2,6cm.
GROUP: All patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean	SD	t	P	SRS*
Regions																		
RF	0.039	0.014	0.029	-0.095	0.027	0.088	-0.001	0.115	-0.164	-0.041	-0.072	0.005	0.048	-0.001	0.076	-0.0	0.978	9
RST	0.016	-0.017	-0.011	-0.063	0.082	0.074	-0.050	0.065	-0,211	0.058	-0.074	-0.006	0.112	-0.002	0.086	-0.1	0.938	9
RMT	0.037	-0.053	0.019	-0.049	0.028	-0.087	-0.002	-0.034	0.027	0.032	-0.097	0.028	-0.066	-0.017	0.049	-1.2	0.265	-35
RO	0.075	-0.043	0.128	-0.010	0.067	0.017	-0.091	-0.001	-0.131	0.050	-0.075	0.088	-0.001	0.006	0.076	0.3	0.804	5
LF	0.039	0.027	0.019	-0.104	0.035	-0.002	-0.052	0.034	-0.174	0.049	-0.102	-0.087	-0.001	-0.025	0.071	-1.2	0.255	-25
LST	0.031	0.070	0.162	-0.162	0.038	0.048	0.044	0.023	-0.063	-0.078	-0.111	0.004	0.129	0.010	0.092	0.4	0.708	15
LMT	-0.007	-0.053	-0.006	-0.075	-0.013	0.097	0.116	-0.074	-0.075	0.112	-0.168	0.013	0.087	-0.004	0.087	-0.1	0.888	-1
LO	0.067	0.007	0.025	0.016	-0.022	0.043	0.063	0.058	-0.182	0.009	-0.063	0.053	0.035	0.008	0.068	0.4	0.676	36
ACG	0.003	-0.024	0.085	0.081	0.134	0.086	0.043	0.036	-0.018	0.134	-0.040	0.104	0.117	0.057	0.061	3.2	0.007	71
PCG	0.068	0.051	0.051	-0.058	0.029	0.026	0.056	0.100	-0.065	0.031	-0.006	0.035	0.068	0.030	0.048	2.2	0.051	51
RBG	0.018	0.029	-0.002	-0.050	0.115	-0.004	0.224	0.055	-0.068	0.030	-0.089	-0.037	0.041	0.020	0.082	0.8	0.416	15
LBG	0.006	0.034	0.162	-0.157	0.016	0.034	0.102	0.099	-0.069	0.029	-0.046	0.001	0.032	0.019	0.081	0.8	0.437	33

*SRC= Signed rank sum

KEY:

RF	=	Right Frontal	LMT	=	Left Medial Temporal
RST	=	Right Superior Temporal	LO	=	Left Occipital
RMT	=	Right Medial Temporal	ACG	=	Anterior Cingulate Gyrus
RO	=	Right Occipital	PCG	=	Posterior Cingulate Gyrus
LF	=	Left Frontal	RBG	=	Right Basal Ganglia
LST	=	Left Superior Temporal	LBG	=	Left Basal Ganglia

Table X: Differences between pre- and post-treatment cerebellar ratios at OM + 4,6cm.
GROUP: All patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean	SD	t	P	SRS*
Regions																		
RF	-0.030	0.017	0.080	-0.040	-0.026	0.028	0.061	-0.039	-0.148	-0.094	-0.021	-0.052	0.154	-0.009	0.078	-0.4	0.706	-17
RP	0.035	0.001	0.138	0.005	0.099	0.089	0.053	0.020	-0.077	0.005	-0.030	-0.041	0.062	0.028	0.060	1.6	0.139	47
RO	0.021	-0.006	-0.005	-0.003	0.079	0.036	0.001	0.032	-0.034	-0.066	-0.046	0.032	-0.023	0.002	0.039	0.1	0.895	-3
LF	0.055	0.014	0.096	-0.067	0.048	0.041	0.020	0.033	-0.049	-0.025	-0.036	0.053	-0.007	0.013	0.048	1.0	0.348	27
LO	0.044	-0.074	0.073	0.030	0.068	-0.003	-0.065	-0.028	-0.093	-0.089	-0.064	-0.005	-0.061	-0.013	0.059	-1.2	0.251	-35
LP	0.047	-0.026	0.109	0.007	0.024	0.070	-0.011	0.092	-0.138	0.064	-0.072	0.018	-0.018	0.037	0.068	0.7	0.526	23
ACG	0.013	-0.018	0.065	-0.043	0.135	0.11[illegible]	0.117	0.105	-0.052	0.042	-0.069	0.022	0.053	0.027	0.069	1.9	0.087	47
PCG	0.096	0.135	0.072	-0.059	0.063	0.06[illegible]	0.009	-0.006	-0.098	0.026	-0.096	0.113	0.031	0.028	0.075	1.2	0.238	37

*SRC= Signed rank sum

KEY:

RF	=	Right Frontal	LO	=	Left Occipital
RP	=	Right Parietal	ACG	=	Anterior Cingulate Gyrus
RO	=	Right Occipital	PCG	=	Posterior Cingulate Gyrus
LF	=	Left Frontal			
LP	=	Left Parietal			

Table XI: Differences between pre- and post-treatment cerebellar ratios at OM + 5,6cm.
GROUP: All patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean	SD	t	P	SRS*
Regions																		
RF	-0.004	0.081	0.022	-0.040	0.048	0.044	0.119	-0.032	-0.087	-0.038	-0.093	-0.023	0.108	0.008	0.069	0.4	0.694	11
RP	-0.022	0.059	-0.031	0.054	0.095	0.075	0.082	0.034	-0.152	0.062	-0.059	-0.019	0.064	0.019	0.071	0.9	0.382	41
RPO	0.037	-0.054	0.005	0.064	0.047	-0.068	0.017	0.065	-0.099	-0.054	-0.065	0.045	-0.027	-0.007	0.057	-0.4	0.693	-15
LF	0.002	-0.003	-0.005	-0.177	0.002	0.101	-0.026	0.068	-0.138	-0.059	-0.003	0.042	-0.023	-0.012	0.066	-0.6	0.534	-28
LP	0.026	-0.003	0.024	-0.095	0.100	0.069	-0.018	0.135	-0.052	0.114	-0.086	0.076	-0.035	0.020	0.076	0.9	0.387	25
LPO	0.122	0.011	0.052	-0.041	0.010	0.094	-0.019	0.104	-0.053	0.065	-0.051	0.057	0.027	0.029	0.059	1.7	0.114	47
SCG	-0.001	0.018	0.041	-0.143	-0.022	-0.029	0.058	0.043	-0.088	0.089	-0.091	-0.030	0.053	-0.008	0.068	-0.4	0.700	-5

*SRC= Signed rank sum

KEY:

RF	=	Right Frontal	LO	=	Left Occipital
RP	=	Right Parietal	LPO	=	Left Parieto-Occipital
RPO	=	Right Parieto-Occipital	SCG	=	Superior Cingulate Gyrus
LF	=	Left Frontal			

Table XII: Differences between pre- and post-treatment cerebellar ratios at OM + 2,6cm
GROUP: Responding patients

Patient no.	1	3	6	9	10	12	13	Mean	SD of sample	t	P	signed rank sum
Regions												
RF	0.039	0.029	0.088	-0.164	-0.041	0.005	0.048	0.001	0.033	0.020	0.985	6
RST	0.016	-0.011	0.074	-0.211	0.058	-0.006	0.112	0.004	0.105	0.104	0.921	8
RMT	0.037	0.019	-0.087	0.027	0.032	0.028	-0.066	-0.001	0.052	-0.061	0.953	2
RO	0.075	0.128	0.017	-0.131	0.050	0.088	-0.001	0.032	0.084	0.940	0.384	12
LF	0.039	0.019	-0.002	-0.174	0.049	-0.087	-0.001	-0.022	0.080	-0.688	0.517	-4
LST	0.031	0.162	0.048	-0.063	-0.078	0.004	0.129	0.033	0.090	0.902	0.402	10
LMT	-0.007	-0.006	0.097	-0.075	0.112	0.013	0.087	0.031	0.069	1.121	0.305	14
LO	0.067	0.025	0.043	-0.182	0.009	0.053	0.035	0.007	0.086	0.204	0.845	14
ACG	0.003	0.085	0.086	-0.018	0.134	0.104	0.117	0.073	0.058	3.086	0.021	24
PCG	0.068	0.051	0.026	-0.065	0.031	0.035	0.068	0.031	0.045	1.658	0.148	18
RBG	0.018	-0.002	-0.004	-0.068	0.030	-0.037	0.041	-0.003	0.039	-0.200	0.848	-2
LBG	0.006	0.162	0.034	-0.0691	0.029	0.001	0.032	0.028	0.069	0.986	0.362	16

KEY:

RF	=	Right Frontal	LMT	=	Left Medial Temporal
RST	=	Right Superior Temporal	LO	=	Left Occipital
RMT	=	Right Medial Temporal	ACG	=	Anterior Cingulate Gyrus
RO	=	Right Occipital	PCG	=	Posterior Cingulate Gyrus
LF	=	Left Frontal	RBG	=	Right Basal Ganglia
LST	=	Left Superior Temporal	LBG	=	Left Basal Ganglia

Table XIII: Differences between pre- and post-treatment cerebellar ratios at OM + 4,6cm
GROUP: Responding patients

Patient no.	1	3	6	9	10	12	13	Mean	SD of sample	t	P	signed rank sum
Regions												
RF	-0.030	0.080	0.028	-0.148	-0.094	-0.052	0.154	-0.009	0.104	-0.215	0.837	-4
RP	0.035	0.138	0.041	-0.077	-0.005	-0.041	0.062	0.030	0.075	0.990	0.360	12
RO	0.021	-0.005	0.036	-0.034	-0.066	0.032	-0.023	-0.005	0.038	-0.354	0.736	-4
LP	0.069	0.072	0.029	0.057	0.023	0.081	0.054	0.055	0.022	6.175	0.001	28
LF	0.040	0.120	0.052	-0.155	-0.073	0.026	-0.068	-0.008	0.094	-2.214	0.837	-4
LO	0.047	0.109	0.070	-0.138	0.064	0.018	-0.018	0.022	0.081	0.659	0.535	12
ACG	0.013	0.065	0.111	-0.052	0.042	0.022	0.053	0.036	0.050	1.766	0.128	20
PCG	0.096	0.072	0.066	-0.098	0.026	0.113	0.031	0.044	0.070	1.525	0.178	16

KEY:

RF	=	Right Frontal	LF	=	Left Frontal
RP	=	Right Parietal	LO	=	Left Occipital
RO	=	Right Occipital	ACG	=	Anterior Cingulate Gyrus
LP	=	Left Parietal	PCG	=	Posterior Cingulate Gyrus

Table XIV: Differences between pre- and post-treatment cerebellar ratios at OM + 5,6cm
GROUP: Responding Patients

Patient no.	1	3	6	9	10	12	13	Mean	SD of sample	t	P	signed rank sum
Regions												
RF	-0.004	0.022	0.044	-0.087	-0.038	-0.023	0.108	0.003	0.063	0.120	0.098	0
RP	-0.022	-0.031	0.075	-0.152	0.062	-0.019	0.064	-0.003	0.080	-0.099	0.924	2
RPO	0.037	0.005	-0.068	-0.099	-0.054	0.045	-0.027	-0.023	0.054	-1.033	0.341	-12
LF	0.002	-0.005	0.101	-0.138	-0.059	0.042	-0.023	-0.011	0.075	-0.365	0.728	-6
LP	0.026	0.024	0.069	-0.052	0.114	0.076	-0.035	0.032	0.060	1.292	0.244	14
LPO	0.122	0.052	0.094	-0.053	0.065	0.057	0.027	0.052	0.056	2.293	0.062	22
SCG	-0.001	0.041	-0.029	-0.088	0.089	-0.030	0.053	0.005	0.060	0.214	0.837	4

KEY:

RF	=	Right Frontal	LP	=	Left Parietal
RP	=	Right Parietal	LPO	=	Left Parieto-Occipital
RPO	=	Right Parieto-Occipital	SCG	=	Superior Cingulate Gyrus
LF	=	Left Frontal			

Table XV: Differences between pre- and post-treatment cerebellar ratios at OM + 2,6cm
GROUP: Non-responding patients

Patient no.	2	4	5	7	8	11	Mean	SD of sample	t	P	signed rank sum
Regions											
RF	0.014	-0.095	0.027	-0.001	0.115	-0.072	-0.002	0.075	-0.063	0.952	1
RST	-0.017	-0.063	0.082	-0.050	0.065	-0.074	-0.009	0.067	-0.315	0.766	-1
RMT	-0.053	-0.049	0.028	-0.002	-0.034	-0.097	-0.035	0.044	-1.775	0.136	-17
RO	-0.043	-0.010	0.067	-0.091	-0.001	-0.075	-0.026	0.057	-0.998	0.364	-13
LF	0.027	-0.104	0.035	-0.052	0.034	-0.102	-0.027	0.067	-0.902	0.408	-9
LST	0.070	-0.162	0.038	0.044	0.023	-0.111	-0.016	0.096	-0.384	0.717	-1
LMT	-0.053	-0.075	-0.013	0.116	-0.074	-0.168	-0.045	0.094	-1.059	0.338	-11
LO	0.007	0.016	-0.022	0.063	0.058	-0.063	0.010	0.048	0.463	0.663	4
ACG	-0.024	0.081	0.134	0.043	0.036	-0.040	0.038	0.065	1.321	0.244	13
PCG	0.051	-0.058	0.029	0.056	0.100	-0.006	0.029	0.055	1.177	0.292	9
RBG	0.029	-0.050	0.155	0.224	0.055	-0.089	0.047	0.113	0.928	0.396	9
LBG	0.034	-0.157	0.016	0.102	0.099	-0.046	0.008	0.098	0.168	0.860	3

KEY:

RF = Right Frontal
RST = Right Superior Temporal
RMT = Right Medial Temporal
RO = Right Occipital
LF = Left Frontal
LST = Left Superior Temporal
LMT = Left Medial Temporal
LO = Left Occipital
ACG = Anterior Cingulate Gyrus
PCG = Posterior Cingulate Gyrus
RBG = Right Basal Ganglia
LBG = Left Basal Ganglia

Table XVI: Differences between pre- and post-treatment cerebellar ratios at OM + 4,6cm
GROUP: Non-responding patients

Patient no.	2	4	5	7	8	11	Mean	SD of sample	t	P	signed rank sum
Regions											
RF	0.017	-0.040	-0.026	0.061	-0.039	-0.021	-0.008	0.040	-0.437	0.667	-7
RST	0.001	0.005	0.099	0.053	0.020	-0.030	0.025	0.045	1.219	0.277	13
RMT	-0.006	-0.003	0.079	0.001	0.032	-0.046	0.010	0.042	0.512	0.631	1
RO	0.014	-0.067	0.048	0.020	0.033	-0.036	0.002	0.044	0.089	0.932	1
LF	-0.074	0.030	0.068	-0.065	-0.028	-0.064	-0.022	0.058	-0.848	0.435	-7
LST	-0.026	0.007	0.024	-0.011	0.092	-0.072	0.002	0.055	0.098	0.926	-1
LMT	-0.018	-0.043	0.135	0.117	0.105	-0.069	0.038	0.091	0.926	0.397	9
LO	0.135	-0.059	0.063	0.009	-0.006	-0.096	0.008	0.083	0.208	0.844	3

KEY:

RF = Right Frontal
RST = Right Superior Temporal
RMT = Right Medial Temporal
RO = Right Occipital
LF = Left Frontal
LST = Left Superior Temporal
LMT = Left Medial Temporal
LO = Left Occipital

Table XVII: Differences between pre- and post-treatment cerebellar ratios at OM + 5,6cm
GROUP: Non-responding patients

Patient no.	2	4	5	7	8	11	Mean	Sd of sample	t	P	signed rank sum
Regions											
RF	0.081	-0.040	0.048	0.119	-0.032	-0.093	0.014	0.081	0.379	0.720	5
RP	0.059	0.054	0.095	0.082	0.034	-0.059	0.044	0.055	1.803	0.131	15
RPO	0.071	0.004	0.039	-0.018	-0.091	-0.050	-0.007	0.059	-0.280	0.791	-3
LF	-0.003	-0.117	0.002	-0.026	0.068	-0.003	-0.013	0.060	-0.495	0.642	-9
LP	-0.003	-0.095	0.100	-0.018	0.135	-0.086	0.006	0.095	0.131	0.901	1
LPO	0.011	-0.041	0.010	-0.019	0.104	-0.051	0.002	0.056	0.094	0.929	-3
SCG	0.018	-0.143	-0.022	0.058	0.043	-0.091	-0.023	0.080	-0.065	0.547	-5

KEY:

RF = Right Frontal
RP = Right Parietal
RPO = Right Parieto-occipital
LF = Left Frontal
LPO = Left Parietal-occipital
SCG = Superior Cingulate Gyrus

When the differences of ^{99m}Tc-HMPAO uptake ratios were considered in both pre-ECT and post-ECT studies in the whole group of subjects (n = 13), significant differences were observed in the transaxial brain slices at 2.6 cm and 4.6 cm above the OML. In the slice 2.6cm above the OML, the anterior cingulate gyrus showed difference in pre- as compared to post-ECT ($p < 0.022$). The difference in the slice 4.6 cm above the OML was noted in the left frontal lobe ($p < 0.048$).

No differences were observed in the assessment oin the assessment of the rCBF in both pre-ECT and post-ECT studies in terms of polarity of the illness. Tables XVIII and XXIV show data of ECT responders and non responders.

TABLE XVIII

Uptake ratios (mean ± s.d) in all patients at 2.6 cm

Region	Before ECT	After ECT	Significance
Frontal	0.744 ± 0.060	0.756 ± 0.810	not significant
Superior temporal	0.770 ± 0.054	0.774 ± 0.075	not significant
Medial temporal	0.783 ± 0.038	0.774 ± 0.063	not significant
Occipital	0.772 ± 0.060	0.780 ± 0.052	not significant
Anterior cingulate gyrus	0.676 ± 0.062	0.739 ± 0.079	< 0.022
Posterior cingulate gyrus	0.075 ± 0.053	0.793 ± 0.049	not significant

TABLE XIX

Uptake ratios (mean ± s.d) in all patients at 4.6 cm

Region	Before ECT	After ECT	Significance
Frontal (Right)	0.768 ± 0.074	0.762 ± 0.072	not significant
Frontal (Left)	0.713 ± 0.039	0.742 ± 0.063	<0.048
Parietal	0.744 ± 0.041	0.752 ± 0.060	not significant
Occipital	0.729 ± 0.051	0.073 ± 0.039	not significant
Anterior cingulate gyrus	0.739 ± 0.062	0.742 ± 0.038	not significant
Posterior cingulate gyrus	0.725 ± 0.061	0.728 ± 0.046	not significant

TABLE XX

Uptake ratios (mean ± s.d) in all patients at 5.6 cm

Region	Before ECT	After ECT	Significance
Frontal	0.744 ± 0.043	0.753 ± 0.062	not significant
Parietal	0.703 ± 0.052	0.701 ± 0.033	not significant
Parieto-occipital	0.719 ± 0.060	0.706 ± 0.054	not significant
Superior cingulate gyrus	0.770 ± 0.029	0.786 ± 0.071	not significant

TABLE XXI

Uptake ratios (mean ± s.d) in 7 Responders and 6 Nonresponders to ECT at 2.6 cm above the orbitomeatal line

	Left Hemisphere			Right Hemisphere		
Region	Before ECT	After ECT	Significance	Before ECT	After ECT	Significance
Responders						
Frontal	0.75 ± 0.059	0.73 ± 0.010	ns	0.78 ± 0.055	0.78 ± 0.081	ns
Sup temporal	0.78 ± 0.062	0.81 ± 0.078	ns	0.79 ± 0.050	0.80 ± 0.088	ns
Med temporal	0.78 ± 0.056	0.81 ± 0.092	ns	0.81 ± 0.046	0.81 ± 0.027	ns
Occipital	0.78 ± 0.068	0.79 ± 0.057	ns	0.78 ± 0.064	0.81 ± 0.049	ns
Basal ganglia	0.82 ± 0.050	0.84 ± 0.110	ns	0.83 ± 0.056	0.82 ± 0.065	ns
Nonresponders						
Frontal	0.72 ± 0.061	0.69 ± 0.057	ns	0.72 ± 0.059	0.72 ± 0.078	ns
Sup temporal	0.74 ± 0.076	0.73 ± 0.046	ns	0.76 ± 0.044	0.75 ± 0.061	ns
Med temporal	0.76 ± 0.051	0.72 ± 0.054	ns	0.78 ± 0.035	0.74 ± 0.049	ns
Occipital	0.76 ± 0.048	0.77 ± 0.034	ns	0.77 ± 0.054	0.74 ± 0.061	ns
Basal ganglia	0.77 ± 0.050	0.78 ± 0.079	ns	0.78 ± 0.043	0.82 ± 0.067	ns

ECT = Electroconvulsive Therapy; ns = not significant; sup = superior, med = medial

TABLE XXI

Uptake ratios (mean ± s.d) in 7 Responders and 6 Nonresponders to ECT at 4.6 cm above the orbitomeatal line

	Left Hemisphere			Right Hemisphere		
Region	Before ECT	After ECT	Significance	Before ECT	After ECT	Significance
Responders						
Frontal	0.80 ± 0.075	0.80 ± 0.080	ns	0.78 ± 0.070	0.77 ± 0.084	ns
Parietal	0.73 ± 0.043	0.77 ± 0.037	0.016	0.76 ± 0.034	0.78 ± 0.075	ns
Occipital	0.71 ± 0.039	0.73 ± 0.078	ns	0.73 ± 0.047	0.73 ± 0.031	ns
Nonresponders						
Frontal	0.75 ± 0.069	0.76 ± 0.062	ns	0.77 ± 0.075	0.75 ± 0.058	ns
Parietal	0.69 ± 0.018	0.69 ± 0.046	ns	0.74 ± 0.043	0.76 ± 0.062	0.062
Occipital	0.71 ± 0.042	0.71 ± 0.036	ns	0.74 ± 0.026	0.75 ± 0.039	ns

ECT = Electroconvulsive Therapy; ns = not significant.

TABLE XXII

Uptake ratios (mean ± s.d) in 7 Responders and 6 Nonresponders to ECT at 5.6 cm above the orbitomeatal line

	Left Hemisphere			Right Hemisphere		
Region	Before ECT	After ECT	Significance	Before ECT	After ECT	Significance
Responders						
Frontal	0.81 ± 0.071	0.80 ± 0.075	ns	0.81 ± 0.065	0.81 ± 0.071	ns
Parietal	0.75 ± 0.059	0.78 ± 0.065	ns	0.79 ± 0.052	0.79 ± 0.073	ns
Parieto-occipital	0.71 ± 0.042	0.76 ± 0.062	ns	0.77 ± 0.050	0.75 ± 0.040	ns
Nonresponders						
Frontal	0.77 ± 0.041	0.76 ± 0.054	ns	0.79 ± 0.087	0.80 ± 0.070	ns
Parietal	0.71 ± 0.068	0.72 ± 0.073	ns	0.72 ± 0.063	0.76 ± 0.061	ns
Parieto-occipital	0.72 ± 0.061	0.73 ± 0.026	ns	0.71 ± 0.020	0.72 ± 0.042	ns

ECT = Electroconvulsive Therapy; ns = not significant.

No significant increase in uptake ratio was observed in the group of responders, except for one region only in slice 4.6cm above the OML [Left parietal ($p = 0.016$)].

No statistically significant change in ^{99m}Tc-HMPAO uptake ratio was observed in the group of patients who did not respond to ECT in Brain Slices 2.6 cm and 5.6 cm while one region showed significant change in slice 4.6 cm above the OML [Right parietal ($p = 0.062$)].

Chapter 7:

DISCUSSION

For ease of understanding, our discussion follows the previous order of this dissertation from the chapter describing patients, materials, methods and data analysis.

7.1 PATIENTS

The selection criteria of the study, especially the age selection and also the history of previous neurologic or psychiatric diseases restricted the study to 15 patients.

In the current literature, the largest study using patients with major depression in pre- and post ECT consisted of 20 patients (Bonne et al, 1996) .

Scott and colleagues (Scott et al, 1994) reported the short-term effects of ECT in major depression in 15 patients, Bojc and colleagues (Bojc et al, 1989) reported the acute change caused by ECT in 8 patients with major depressive disorder, while in a case report, Petrocca et al (1995) documented cerebral perfusion patterns after a course of 12 ECT treatments in a patient with major depression and Cotard's syndrome.

7.2 MATERIALS AND METHODS

7.2.1 ECT Administration

Although ECT can be used in a variety of psychiatric conditions, it is mainly indicated in depression, mania, and schizophrenia.

In severe depression, ECT remains the most effective treatment with 80 - 90% of patients recovering as compared to 60 - 70% of patients on anti-depressants.

Changes in regional cerebral blood flow during and after ECT have been documented. However, the mechanism responsible of these changes is unclear (Personal communication with M.S George)

While cerebral perfusion imaging is widely assessed with SPECT technique, cerebral perfusion patterns in post ECT have received little attention.

This would appear surprising as ECT has been proven to be an effective treatment of severe depression.

In 1989, the study by Bojc and colleagues showed the redistribution of the tracer uptake in the frontal areas and the basal ganglia in patients with major depression, when ^{99m}Tc-HMPAO was used during the acute phase of ECT (Bojc et al, 1989).

In 1994 Scott and co-workers reported on short-term effects of electroconvulsive therapy treatment on the uptake of ^{99m}Tc-exametazine into brain in major depression (Scott et al, 1994). A case report by Petrocca et al (1995) in a patient with major depression and cotard's syndrome was also published when the patient was successfully treated with ECT and the brain imaging showed increased uptake in the regions which had reduced uptake before treatment.

Then, the study by Bonne et al (1996) demonstrated findings which lead to the conclusion that the reduced cerebral blood flow in depression was a state-related property which can be reversed by successful treatment. In that study, 20 patients with major depression were investigated in pre and post ECT treatment with ^{99m}Tc-HMPAO SPECT.

Post ECT brain imaging is unlikely to change patient management. matter. However, Bonne et al (1996) suggests the use of SPECT imaging as a prognostic monitor of therapy in severe depression.

7.2.2 Scan acquisition and imaging processing

Taking into account the in-vitro instability of ^{99m}Tc-HMPAO, the administration of the tracer was within 10 minutes of its preparation. Some retrospective quality control on the prepared tracer showed the radiochemical purity of greater than 85% which is in line with the requirement for a kit to be used within 30 minutes of reconstitution (Petter et al, 1993).

Before injecting the radiotracer, patients were asked to drink 200 mg of perchlorate diluted in 20 millilitres of water to enhance brain uptake and also minimize the facial soft tissue uptake. all our patients were in a quiet and dimmed room for approximately 30 minutes prior to tracer injection. This protocol is in keeping with the worldwide actual trend when performing SPECT brain imaging (Bonne et al, 1996).

The acquisition parameters and images processing were in line with the routine clinical use of brain imaging in our department.

7.3 DATA ANALYSIS

The visual assessment of brain studies has been a long aged method of interpretation of most studies. The combination with a quantitative assessment finds its place mainly in research work.

In the quantification of interictal metabolic activity in human temporal lobe epilepsy, Henry et al (1990) described the visual image analysis to be more sensitive than quantitation of temporal lobe asymmetry in identifying the seizure focus.

In our study, the semiquantitative method was applied with templates

created at different levels above the OML (2.6 cm, 4.6 cm and 5.6 cm). Similar protocols have been previously used in brain studies by different researchers (Daniela et al, 1998 and Bonne et al, 1996).

The accuracy of the level above the orbitomeatal line (OML) was checked while using point sources made with ^{99m}Tc which were placed 70 mm apart on a line perpendicular to the OML of a particular patient passing through his external auditory meatus whereas the OML was established with point sources made on the canthus and external auditory meatus, allowing accurate localization of the OML.

ROIs generated in different anatomical regions of the templates had the same size. their shape however did not fit the whole anatomical concerned region, in the way previously used by Daniela et al (1988) and Mayberg et al (1994).

Indeed, when ROIs are used to compare their results during control and test condition, the shape of ROIs varies. in some studies they are predetermined and regular whilst in others they are irregular and designed to enclose a specific area.

The relative cerebral count in our study was calculated from the total count per pixel for each ROI. This relative cerebral count was later divided by the mean count rate over the cerebellum to obtain the CBF ratio. Both methods are in keeping with published researches (Camargo et al, 1991; Goldenberg et al, 1989; Lang et al, 1988; Matsuda et al, 1988; Battisstin et al, 1989; and Bonne et al, 1996).

We utilised both visual and quantitative assessments to analyse the data of this study.

7.4 RESULTS

In pre-ECT studies, perfusion abnormalities were mainly visualised in frontal and temporal areas. Less changes were noted in basal ganglia, anterior cingulate gyrus, occipital and parietal areas. These findings are in keeping with published literature in major depression (Yazici et al, 1992; Austin et al, 1992; Mayberg et al, 1994; and Thomas et al, 1993). They also correlate with the results of Mozley et al (1996) who looked at cerebral HMPAO SPECT in patients with major depression (n = 19) and healthy volunteers (n = 16) where the distribution of HMPAO was more variable in patients than in controls and also that asymmetries between homotopic regions of the limbic system were more pronounced in patients than in controls.

In a study by Ito et al (1996) similar results were also noted when 17 patients with major depression and 9 age-matched normal control subjects had undergone HMPAO brain SPECT. In fact, Significant decreases in CBF in the prefrontal cortices, limbic systems and paralimbic areas were observed in depression group compared with the normal control group.

In post-ECT of our study, patients who responded to ECT, except for one, showed visual increased cerebral perfusion, whereas patients who did not respond to ECT showed unchanged patterns. These findings correlate with the results in studies of brain imaging post depression treatment (Goodwin et al, 1993; Petrocca et al, 1995; Bojc et al, 1996).

When we applied the semiquantitative method in the group of our patients, significant change was noted in the left frontal and the anterior cingulate gyrus in keeping with the results of Bonne et al (1996) and Goodwin et al (1993).

There were no statistically significant chabges in uptake ratios when the quantitative analysis was used in pre-and post ECT studies on responders, except for the parietal area.

These findings partially contrast with the results of Bonne et al (1996) who noted changes also in both anterior and posterior cingulate gyri. However, when Maes and colleagues (1993) looked at the regional cerebral blood flow in 43 depressed subjects and 12 normal control subjects, using individual ROIs for quantitation, they found no significant differences in the distribution of ^{99m}Tc-HMPAO uptake between the two groups.

Our study showed different findings when the visual assessment and the semiquantitative results were considered in patients separated into groups of ECT responders and non-responders.

The differences between the two ways of results assessments triggered our attention to look for possible causes. We therefore reviewed the images and noted that most of the changes were visualised on the temporal and sagital slices. the transaxial oblique slices showed more heterogeneity of distribution which may count for less differences in terms of count in the ROIs when the quantitation was applied. In our view, the differences noted between the two ways of assessing data could be multifactorial.

Firstly, the slices showing most changes of perfusion patterns (temporal and sagital) were not submitted to quantitative evaluation. The reason being that most quantitative brain studies use ROIs placed over the transaxial oblique slices. The rationale behind the use of these slices could be explained by the fact that symmetrical comparison of ROIs can be done with a degree of confidence as they derived from anatomical plane used during the reconstruction (the orbitomeatal line).

Secondly the sample used might be small to show the significance of count differences between the pre- a· ·l post treatment studies. The largest study with

pre- and post ECT studies comprised only twenty patients, but showed very significant changes in three different regions (Bonne et al, 1996).

Thirdly, the ROIs used on templates though similar in size, do not fit the whole particular region examined. In other words, the ROI is placed in a particular region (e.g. frontal) but does not cover the whole frontal area in a particular slice used for quantitation. However, small ROIs have been used in different studies before. Mayberg et al (1994) studied 13 patients with severe unipolar depression and 11-age-matched non depressed controls. The differences in the rCBF volumes were significant but the study included two different groups of subjects and the visual assessment was not used.

Yet in another study by Daniela et al (1988), small ROIs were also used in a study on sixteen patients with Alzheimers disease (AD) in early clinical phase and in 16 healthy elderly controls. The mean values ± s.d of the rCBF showed significantly reduced perfusion in patients with AD compared with the elderly normal subjects. Here again we have two different groups of subjects without the visual assessment correlation. When both methods were used in human temporal lobe epilepsy, Henry et al (1990) found that visual image analysis was more sensitive than quantitation of temporal lobe asymmetry to identify the seizure focus.

We will therefore suggest that the discrepancy noted between the visual assessment and the semiquantitative correlation brings the need for future studies, though the implication of ROI size. This project should not only be focussed in depression or in pre- and post-ECT therapy rather than any neuropsychiatric brain imaging with preferably a control group in view of determining the cause of differences and maybe reconcile the discrepancy noted in our study.

Furthermore, views of Takashi and colleagues (Takashi et al, 1996) to improve quantitative accuracy in brain SPECT should also be considered. Knowing that photon attenuation is one of the most important factors degrading the quantitative accuracy of SPECT images, they designed and evaluated a

simultaneous emission and transmission scan system for brain SPECT using the triple energy window (TEW) scatter composition method and for beam collimators. They concluded from their results that the proposed system improves quantitative accuracy in brain SPECT.

Chapter 8:

CONCLUSION

The following trends were observed in our study:

- Visually reduced rCBF in Temporal and Frontal areas for ^{99m}Tc-HMPAO uptake appear to relate to depression and a reversed pattern was recorded after successful treatment.

- SPECT with ^{99m}Tc-HMPAO can be used as a prognostic monitor of therapy.

- Although generally implicated in depressed patients, no significant perfusion patterns of changes in the Anterior Cingulate Gyrus was observed in our group of patients.

- The perfusion decreased noted in the occipital and parietal regions are not predictive of depression.

- There is a great need for further studies to look at the possible causes of differences between the visual and the quantitative assessments of cerebral perfusion. We should however keep in mind that publications where the two methods are compared are lacking while one would think that both methods should correlate. Henry et al (1990) showed the superiority of the visual assessment of the epileptic focus over the quantitative method in patients with temporal lobe epilepsy. We conclude that more studies in different diseases should be done and semiquatitative analysis be conducted.

EFERENCES

1. Aggleton, J.P. and Mishkin, M. 'The amygdala: Sensory gateway to the emotions.' New York : Academic Press, 1986 : 281-299

2. Altshuler, L., Conrad, A., Hauser, P.,et al. 'Reduction of temporal lobe volume in bipolar disorder: a preliminary report of MRI.' Archives of General Psychiatry, 48 : 482-3, 1991

3. Austin, M.P., Dougall, N., Murray, C., et al. 'Single photon emission tomography with ^{99m}Tc-exametazime in major depression and the pattern of brain activity underlying the psychotic/neurotic continum.' Journal of Affective Disorders, 29 : 31-43, 1992

4. Battisstin, L., Pizzolato, G, Dam, M., et al. 'Emission computed tomography studies with ^{99m}Tc-HMPAO in dementia: effects of acute administration of L-acetylcarnitin.' European Neurology, 29 : 261-5, 1989

5. Baxter, L.R., Schartz J.M., Pheps, M.E.,et al. 'Reduction of prefrontal cortex glucose metabolism common to three types of depression.' Archives of General Psychiatry, 46 : 243-250, 1989

6. Bench, C.J., Friston, K.J., Brown, R.G.,et al. 'The anatomy of melancholia - focal abnormalities of cerebral blood flow in major depression.' Psychological Medicine, 22 : 607-615, 1992

7. Bench, C.J., Friston, K.J., Brown, R.G., et al. 'Regional cerebral blood flow in depression measured by position emission tomography: the relationship with clinical dimensions.' Psychological Medicine, 23 : 579-590, 1993

8. Bojc, M., Medved, V., Basic, M.,et al. 'Acute effect of electroconvulsive therapy on brain perfusion assessed by ^{99m}Tc-hexametyhl propyleneamine oximine and single photon emission computed tomography.' Acta Psychiatrica Scandinavia, 80 : 421-6, 1989

9. Bonne, O.,Krausz, Y., Shapira, B., et al. 'Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy.' Journal of Nuclear Medicine, 37 : 1075-1080, 1996

10. Camargo, E.E., Rivera, L.H., Sostre, S.,et al. 'Cerebral activation during the stroop test identified by brain SPECT imaging.' European Journal of Nuclear Medicine, 18 : 595 (Abstract), 1991

11. Catafau, A.M., Lomena, F.L., Pavia, J., et al. 'Regional cerebral blood flow pattern in normal young and aged volunteers: a ^{99m}Tc-HMPAO SPECT study.' European Journal of Nuclear Medicine, 23 :1329-1337, 1996

12. Coffey, C.E., Figiel, G.S., Djang, W.T.,et al. 'Leukoencephalopathy in elderly depressed patients referred for ECT.' Biological of Psychiatry, 24 : 143-161, 1988

13. Coffey, C.E., Wilkinson, W.E., Weiner, R.D.,et al. 'Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study.' Archives of General Psychiatry, 50 : 7-16, 1993

14. Daniela, P., Rittonion, D.P., Giuseppe, V.,et al. 'Technetium - ^{99m}Tc-HMPAO SPECT study of regional cerebral perfusion in early Alzheimer's disease.' Journal of Nuclear Medicine, 29 : 1507 - 1514, 1988

15. Dolan, R.J., Bench, C.J., Lidlle, P.F.,et al. 'Dorsolateral prefrontal cortex dysfunction in the major psychoses: symptom or disease specificity?' Journal of Neurology, Neurosurgery and Psychiatry, 56 : 1290-4, 1993

16. George, M.S. Introduction: 'The Emerging Neuroantomy of Depression'. Psychiatric Annals, 24: 635-6, 1994

17. Goldenberg, G., Pedroka, I., Steiner, M.,et al. 'Regional Cerebral blood flow patterns in visual imagery.' Neuropsychologia, 27 : 641-664, 1989

18. Goldenberg, G., Podroka, I., Uhl, F.,et al. 'SPECT of regional cerebral blood flow.' Neuropsychologia, 27 : 1315-1328, 1989

19. Goodwin, G.M., Austin, M.P., Dougall, N.,et al. 'State changes in brain activity shown by the uptake of ^{99m}Tc-exametazine with single photon emission tomography in major depression before and after treatment.' Journal of Affective Disorders, 29 : 243-253, 1993

20. Gottschalk, A., Hoffer, P.B., and Potchen, E.J. Diagnostic Nuclear Medicine. Williams & Wilkins, 125-7. 2V

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

22. Harold, A.S., Prudic, J., Devanard, D.P.,et al. 'The impact of medication re stance and continuation pharmacotherapy on relapse following response to ECT in major depression.' Journal of Clinical Psychopharmacology, 10, 1990

23. Henry, T.R., Mazziotta, J.C., Chritenson, P.D.,et al. 'Quantifying interictal metabolic activity in human temporal lobe epilepsy.' Journal of Cerebral Blood Flow Metabolism, 10 : 748-757, 1990

24. Imlah, N.W., Ryan, E., and Harrington, J.A. 'The influence of antidepressant drugs on the response to electroconvulsive therapy and on subsequent relapse rates.' Neuro-psychopharmacology, 4 : 438-442, 1965

25. Ito, H., Kawashima, R., Awata, S.,et al. 'Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique.' Journal of Nuclear Medicine, 37 : 410-4, 1996

26. Kaplan, H.I., Benjamin, J., and Sadock, M.D. Comprehensive Book of Psychiatry. williams & Wilkins, 656-661. 2V

27. Ibid., pp. 1126-1146

28. Ibid., pp. 2129-2140

29. Kellner, C.H., Rubinow, D.R., and Post, R.M. `cerebral ventricular size and cognitive impairement in depression. Journal of Affective Disorders, 10:215-219, 1986

30 Ketter, T.A. and George, M.S. 'Activation studies in mood disorders.' Psychiatric Annals, 24 : 648-652, 1994

31. Ketter, T.A., George, M.S., Andreason, P.J.,et al. 'Depression and frontal regional cerebral metabolic rates of glucose correlate inversely.' APA New Research Abstracts, 1994

32. Kumar, A., Mozley, P.D., Dunhan, C.,et al. 'Semiquantitative I^{123} IMP SPECT Studies in late onset depression before and after treatment.' International Journal of Geriatric Psychiatry, 6 : 775-7, 1991

33. Lang, W., Pedroka, I., Suess, E.,et al. 'Single photon emission tomography during and between seizures.' Journal of Neurology, 235 : 277-289, 1988

34. Levitt, M., Spector, S., Sjoerdoman, R.,et al. 'Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea pig heart.' Journal of Pharmacological Experiments, 148 : 1-8, 1965

35. Maes, M., Dierckx, R., Meltzer, H.Y.,et al. 'Regional cerebral blood flow in unipolar depression measured with ^{99m}Tc-HMPAO single photon emission computed tomography: Negative findings.' Psychiatry Research in Neuroimaging, 50 : 77-88, 1993

36. Matsuda, H., Higashi, S., Asli, I.N., et al. 'Evaluation of cerebral collateral circulation by technetium-99m HMPAO brain SPECT during matas test: report of three cases.' Journal of Nuclear Medicine, 29 : 1724-9, 1988

37. Mayberg, H.S., Starkstein, S.E., Sadzot, B.,et al. 'Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease.' Annals of Neurology, 28 : 57-64, 1990

38. Mayberg, H.S., Lewis, P.J., Regenold, W.,et al. 'Paralimbic hypoperfusion in unipolar depression.' Journal of Nuclear Medicine, 35 : 929-934, 1994

39. Mayeux, R. 'Emotional changes associated with basal ganglia disorders.' New York: Guilford Press, 1983 : 141-164

40. Mindham, R.H.S., Howland, C., and Shephred, M. 'An evaluation of continuation therapy with tricyclic antidepressants in depressive illness.' Psychological Medicine, 3 : 5-17, 1973

41. Mozley, P.D., Hornig, R.M., Woda, A.M.,et al. 'Cerebral HMPAO SPECT in patients with major depression and healthy volunteers.' Progress in Neuro-psychopharmacology and Biological Psychiatry, 20 : 445-458, 1996

42. Murray, I.P.C., and Ell, P.J. Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 1315-1346. 2V

43. Nobler, M.S., Sackein, H.A., Prohovnic, I., et al. `Regional cerebral blood flow in mood disorders`. Archives of General Psychiatry, 51: 884-897, 1994

44. Papez, J.W. 'A proposed mechanism of emotion.' Archives of Neurology and Psychiatry, 38 : 725-743. 1937

45. Petrocca, G., Migliorelli, R., Vazquez, S., et al. 'SPECT findings before and after ECT in a patient with major depression and cotard's syndrome.' Journal of Neuro-psychiatry and Clinical Neurosciences, 7 : 505-7, 1995

46. Petter, S., Bower, G.R., Dollimore, L.A.,et al. 'A method for stabilising technetium-99m exarnetazime prepared from a commercial kit.' European Journal of Nuclear Medicine, 20 : 661-6, 1993

47. Prien, R.F., Klett, C.J., and Coffey, E.M. Jr. 'Lithium Carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness.' Archives of General Psychiatry, 29 : 420-5, 1973

48. Scott, A.I.F., Dougall, N., Ross, M.,et al. 'Short-term effects of electroconvulsive treatment on the uptake of ^{99m}Tc-exametazime into brain in major depression shown with single photon emission tomography.' Journal of Affective Disorders, 30 : 27-34, 1994

49. Sharp, P.F., Smith, F.W., Gemmel, H.G.,et al. 'Technietium-99m HMPAO stereoisomers as potential agent for imaging regional cerebral blood flow.' Journal of Nuclear Medicine, 25 : 171-7, 1986

50. Silfverskiold, P., Gustafson, L., Risberg, L., et al. `Acute and Late effects of Electroconvulsive Therapy: clinical outcome of regional cerebral blood flow and electroencephalogram'. Annals of New York Academy of Sciences, 462: 236-248

51. Starkstein, S.E., and Robinson, R.G. 'Depression in Neurologic disease.' Hopkins University Press, 1993

52. Takashi, I., et al. 'Evaluation of SPECT quantification of simultaneous emission and transmission imaging of the brain using a multidetector SPECT system with the TEW scatter compensation method and fan-beam collimator.' European Journal of Nuclear Medicine, 23 : 1292-9, 1996

53. Thomas, P., Vaiva, G., Samaille, E.,et al. 'Cerebral blood flow in major depression and dysthymia.' Journal of Affective Disorders, 29 : 235-242, 1993

54. Thomas, P., Vaiva, G., Maron, M., et al. 'Variation of cerebral ^{99m}Tc-HMPAO uptake during major depression treatment.' Circulation et Metabolisme du Cerveau, 11 : 15-20, 1994

55. Wing, J.K., Cooper, J.E., and Sartorius, N. 'Measurement and classification of psychiatric symptoms.' Cambridge University Press, 1974

56. Yazici, K.M., Kapucu, O., Erbas, B., et al. 'Assessment of changes in regional cerebral blood flow in patients with major depression using the ^{99m}Tc-HMPAO single photon emission tomography method.' European Journal of Nuclear Medicine, 19 ; 1038-1043, 1992

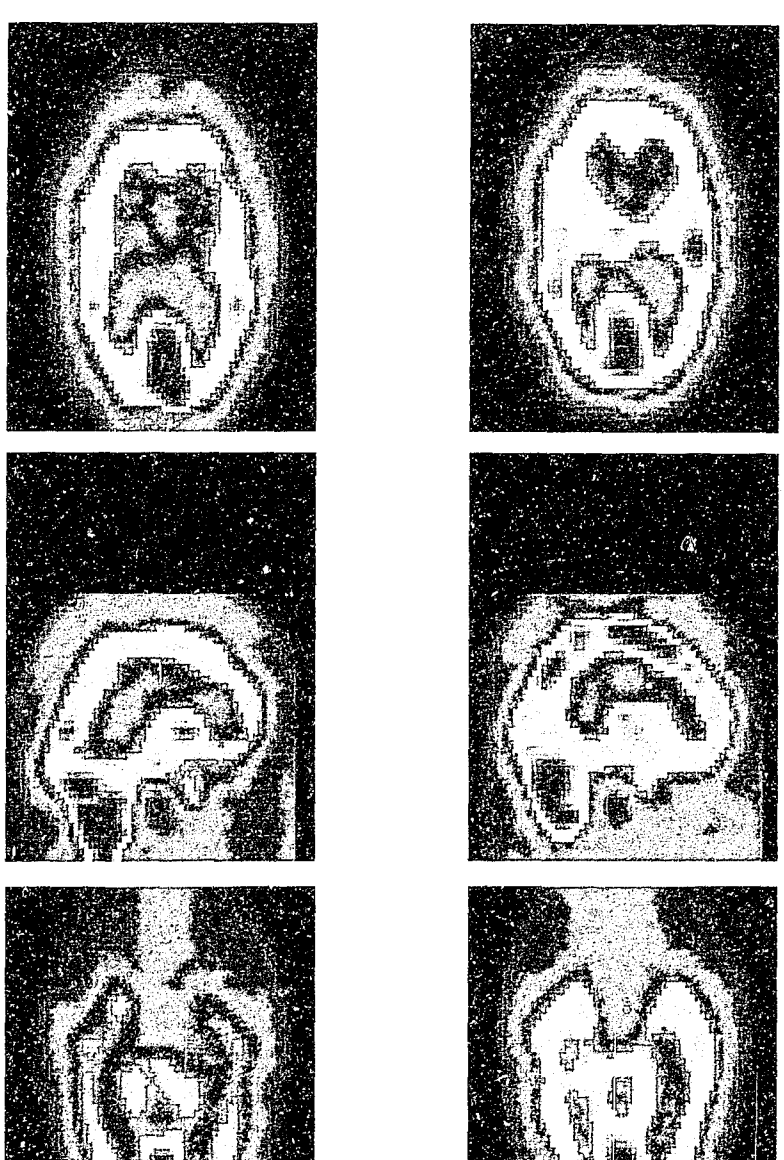
57. Zielinski, R.J., Roose, S.P., Devanand, D.P., et al. 'Cardiovascular complication of ECT in depressed patients with cardiac disease.' American Journal of Psychiatry, 150 : 904-9, 1993

APPENDIX

Selected images of responders and non-responders to the Electroconvulsive Therapy and presented in the following pages.

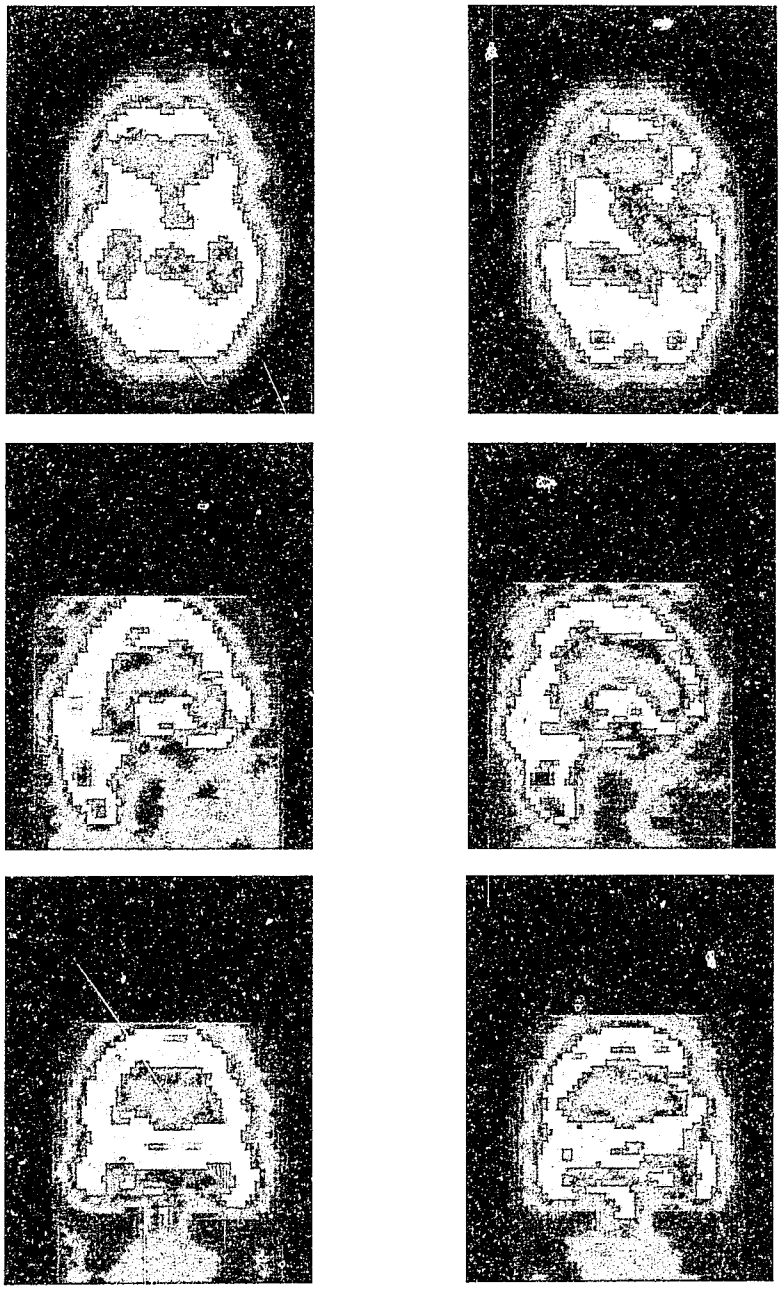
Different cerebral perfusion patterns can be seen in Figures 4,5,6 and 7.

TC-HMPAO



pre ECT **post ECT**

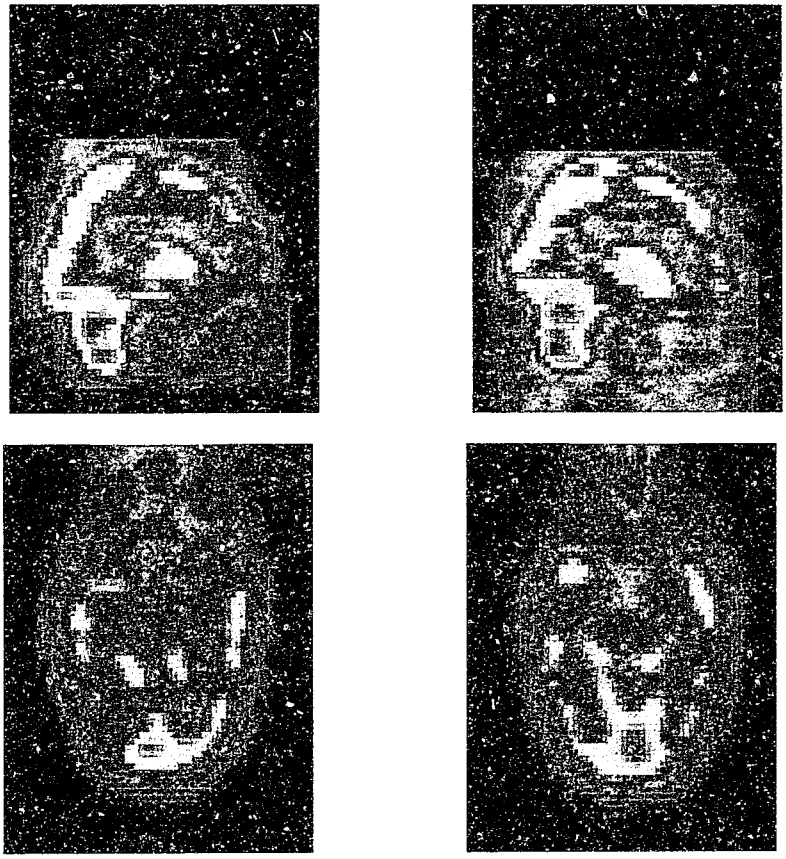
Fig 4: Patient no. 6. Post ECT showing improvement in ACG, BG and temporal lobes.



pre ECT post ECT

Fig 5: Patient no. 4. Post ECT showing worsening of perfusion in frontal lobe mainly. Note: patient became worse in post-treatment period.

TC-HMPAO



pre ECT **post ECT**

Fig 6: Patient no. 2 with unchanged patterns of perfusion in post ECT.

TC-HMPAO

pre ECT **post ECT**

Fig 7: Patient no. 11 showing worsening of perfusion in post ECT. This patient did not respond to ECT and was in PTSD after therapy.

Author Vangu M D T H
Name of thesis Spect Scintigraphic Ic-99M Hmpaq Appearance In Pre- And Post Electroconvulsive Therapy (Ect) In Patients With Major Depression Vangu M D T H 1998

PUBLISHER:
University of the Witwatersrand, Johannesburg
©2013

LEGAL NOTICES:

Copyright Notice: All materials on the University of the Witwatersrand, Johannesburg Library website are protected by South African copyright law and may not be distributed, transmitted, displayed, or otherwise published in any format, without the prior written permission of the copyright owner.

Disclaimer and Terms of Use: Provided that you maintain all copyright and other notices contained therein, you may download material (one machine readable copy and one print copy per page) for your personal and/or educational non-commercial use only.

The University of the Witwatersrand, Johannesburg, is not responsible for any errors or omissions and excludes any and all liability for any errors in or omissions from the information on the Library website.