Imaging the structure and function of limbic and subcortical regions in depression

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"Anatomy is destiny"

(Sigmund Freud, Collected writings 1924)

Dedicated to my wife, my children and to my late father

I declare that:

(i) this thesis has been composed by myself

(ii) it has not been accepted in any previous application for a degree

(iii) the work of which it is a record has been done by myself (my independent contribution as well as the contributions of others have been clearly indicated at the beginning of each Chapter)

(iv) all verbatim extracts have been distinguished by quotation marks, and my sources of information have been clearly acknowledged.

Date 21/6/2000

Summary

Recent imaging studies suggest that there are changes in the anatomy and function of limbic and subcortical structures in depression. However, the evidence is conflicting, possibly reflecting differing symptoms, illness duration, sample ages and aetiologies of depression. The experiments described here provide evidence explaining some of this variability.

The striatum shows anatomical and functional changes associated with depression, suggesting the involvement of dopamine. Using IBZM, a SPET ligand with high dopamine $D_{2/3}$ receptor selectivity, in-vivo striatal $D_{2/3}$ receptor availability was examined in 15 depressed in-patients and 15 matched controls. Depressed patients had increased receptor availability, implying reduced striatal dopaminergic activity in depressed patients. Increased receptor availability was related to objectively measured motor slowing in the depressed group.

Inter-individual variation in IBZM binding may be due to a combination of state and trait effects. Two trait effects were found in controls- sexual dimorphism, with women showing higher receptor availability, and a large effect related to specific personality traits.

Evidence for structural change in depression is conflicting, the strongest being for striatal and frontal lobe volume reductions in unipolar depression. Patients with chronic treatment resistant unipolar depression were examined, as they may be most likely to have structural brain changes.

Voxel based analysis was used to compare the high resolution MRI images of twenty patients with chronic, treatment resistant unipolar depression, with 20 individually matched patients who had recovered and 20 individually matched healthy controls. Only chronically depressed patients exhibited MRI differences. Chronically depressed patients had frontal lobe and right striatal atrophy found using both VBA and conventional volumetry, and also reduced grey matter density in left temporal lobe and left anterior hippocampi. Neocortical changes correlated with the cumulative severity of illness. Medial frontal grey matter reductions correlated with age, psychomotor retardation as well as current and past illness severity in patient groups. Left hippocampal grey matter reductions correlated with reduced episodic verbal memory. Voxel based analysis was a sensitive and complete analysis of MRIs providing results consistent with contemporary hypotheses. Further studies need to examine if these changes represent pre-existing trait or state change, to what extent do they represent biochemical change as opposed to anatomical change, and to what extent they are irreversible. The results challenge the notion of depression being a fully reversible disorder with no structural sequelae.

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List of Abbreviations

↑	increases
↓	decreases
-ve	negative
+ve	positive
ant.	anterior
AVLT	adult verbal learning test
AV5	Number of words recalled after fifth trial
AVT	Total number of words recalled across 5 trials
AVB	Number of words recalled with second list
AV6	Number of words recalled from first list after recalling second list
AVDL	Number of words freely recalled from first list after 30 minutes
AVRC	Number of words recognised as from the first list after 30 mins
bilat.	bilateral
C	Controls
CI	Confidence interval
cing	cingulate
CSF	cerebrospinal fluid
CT	computerised tomography
CTRD	Chronic, treatment resistant depression
DSST	digit symbol substitution test
DWMH	deepwhite matter hyperintensity
EPQ	Eyesenck personality questionairre
ECT	electro-convulsive therapy
GM	grey matter
HPA	hypothalamic-pituitary-adrenal
HD	Huntington's disease
HRSD	Hamilton rating scale for depression
IBZM	^{123}I-3-iodo-methoxybenzamide
inf.	inferior
IQ	Intelligence quotient

L.	left
lat.	lateral
med.	medial
MMSE	minimental state examination
MRI	magnetic resonance imaging
MST	match to sample test. Figure in parenthesis indicates length of delay in seconds
NART	National Adult Reading Test
OML	orbito-meatal line
orb.	orbital
p	probability
PD	Parkinson's disease
PET	Positron emmision tomography
precent	precentral
post.	posterior
PVH	periventricular hyperintensity
R.	right
RD	Recovered depression
ROI	Region of interest
SPET	Single photon emmision tomography
SPM	Statistical parametric mapping
VBA	voxel based analysis
VTA	ventral tegmental area
SAD	seasonal affective disorder
SADS	Schedule for affective disorders and schizophrenia
SD	Standard deviation
SP	sulcal prominence
STRPW	Number of words read out in 2 minutes
STRPP	Percentile score on colour task
STRPT	Time taken to read out word task
STRPWC	
sup.	superior

temp.	temporal
TPQ	Tridimensional personality questionairre
VBR	ventricle to brain ratio
WMH	White matter hyperintensity
WM	white matter

CHAPTER 1:

INTRODUCTION

Chapter 1: Introduction

1.0 This thesis presents work carried out at the MRC Brain Metabolism Unit and University of Edinburgh Department of Psychiatry between 1995 and 1998. Two main imaging experiments were carried out to investigate limbic and subcortical structures in vivo in depression. In the first, dopamine D2/3 receptor availability was examined in fifteen depressed and fifteen healthy controls. In the second experiment, the MRIs of twenty chronic, treatment resistant depressed patients were compared with two individually matched reference groups- twenty healthy volunteers, and twenty patients who had fully recovered from depression.

1.1 Depression is the "common cold" of psychiatry, with a lifetime incidence in community surveys of about 20% (Rorsman *et al*, 1990). It is commonly regarded as a wholly reversible psychiatric illness associated with no lasting neurological change. Its apparent reversibility makes it an ideal experimental paradigm for imaging studies, as it allows within subject comparisons of a condition with no apparent structural change.

1.2 For over 100 years, it has been thought that the regulation of emotions involves limbic and subcortical structures (Broca, 1878). The evidence for this view has largely been based on serendipitous lesion experiments in humans or from experimental animal models, where there have been gross disturbances in cerebral structure and function (Brown & Schlaepfer, 1888; Kluver & Bucy, 1938; Kluver & Bucy, 1939). Logically, it follows that pathological mood changes, such as those found in clinical depression, should be associated with functional and anatomical changes in these areas. However, most mood-disordered patients do not have clearly visible cerebral differences in these areas using conventional structural imaging techniques. This and the natural history of the illness have led to the view that mood disorders are "functional" in nature.

This view has been challenged recently by findings from studies examining the metabolic or perfusion changes *in vivo* during and after recovery from depression. Such studies have found that the perfusion changes in depression may not wholly normalise on recovery (Goodwin *et al*, 1993; Dolan & Goodwin, 1995), suggesting that a structural change may be present. As a result, interest has been rekindled in the quantitative neuroanatomy of limbic and subcortical structures. A number of technological advancements have

been central to this renaissance of interest. First, increasing resolution of structural imaging using MRI has allowed the detection of subtle anatomical change in small structures such as the hippocampus (Sheline *et al*, 1996), which previously could not have been measured with meaningful accuracy. Secondly, more sophisticated methods of image analysis, such as voxel based analysis (VBA), have recently been applied to structural imaging data (Wright *et al*, 1995). VBA has already revolutionised the approach to analysing functional imaging data (Friston, 1994). It has a number of advantages over traditional quantitative region of interest analysis, such as allowing the full use of all imaging data and promises to have a significant impact in the way structural imaging data are analysed and interpreted.

1.3 These initial functional imaging studies have also confirmed that spatially distributed cerebral areas are normally organised into functional networks, and that mood disorders may involve changes in a number of such networks. Symptoms would then arise as a result of disturbed function in these networks. Hence, one approach to understanding the neurobiology of depression is to identify symptoms or clusters of symptoms which may map to specific neuronal systems.

Matching symptoms with networks may be difficult. The syndrome of depression includes many widely diverging symptoms, including anxiety, apathy, psychotic symptoms, and the so-called "biological" symptoms of depression, such as sleep disturbance, appetite change and diurnal variation in mood. Despite this, psychomotor retardation, or slowing of cognitive and motor functions, has been demonstrated repeatedly in severe depression. In fact, some authors regard psychomotor retardation as a core feature of melancholic depression (Widlöcher, 1983; Parker *et al*, 1993). Evidence from perfusion imaging studies provides a candidate system that may be involved in the production of motor retardation. Depressed patients show reduced perfusion in frontal and striatal regions that may correlate with the degree of motor retardation (Austin *et al*, 1992b; Curran *et al*, 1993; Mayberg *et al*, 1994). Fronto-striatal regions are heavily innervated by dopaminergic neurones. Hence, with the availability of dopamine receptor binding SPET ligands, it is now possible to directly test the hypothesis that striatal dopamine may reflect motor retardation in depression.

1.4 Thesis overview

As a starting point, therefore, the neuroanatomy of the brain regions thought to be involved in mood regulation is reviewed in chapter 2. Then, evidence from recent SPET and PET functional imaging studies examining subjects during an induced mood change and examining patients with primary depression are reviewed (Chapter 2). These studies of cerebral perfusion or metabolism are indirect measures of actual change in synaptic neurochemistry, but provide supportive evidence that dopamine may be involved in some of the symptoms of depression. The chapter also summarises the clinical and symptom correlates of perfusion changes during depression and examines whether all perfusion and metabolic changes normalise on recovery.

Chapter 3 describes the first experiment comparing the striatal dopamine D2/3 receptor availability in fifteen clinically depressed in-patients with that in fifteen matched healthy controls. An index of striatal D2/3 receptor availability was derived using ^{123}I-IBZM, a D2/3 receptor SPET ligand with high specificity and moderate affinity. IBZM binding is dependant on the density of striatal D2/3 receptors and on the active competition for binding from the endogenous receptor ligand, dopamine. It was hypothesised that melancholically depressed patients with motor slowing

would show increased receptor availability compared to controls, suggesting reduced endogenous dopamine release. The further hypothesis that receptor availability in the depressed patients reflects psychomotor retardation was tested by correlating objective measures of psychomotor slowing with the binding of IBZM. Finally, personality correlates of receptor availability were examined in the controls, supporting the notion that the striatum, particularly striatal dopaminergic neurones is involved in the regulation of complex human behaviours.

In chapter 4, the evidence for structural change in depression is reviewed. The factors associated with structural change are examined, such as age, age of onset and vascular disease. The argument is developed that treatment resistance and chronicity in depression may be expected to be associated with structural changes.

Chapter five describes the second experiment where the MRI images of twenty patients with chronic, treatment resistant depression (CTRD) were compared with the images from twenty closely matched patients who had recovered and with twenty matched controls. High resolution MRI images were compared using SPM (statistical parametric mapping), a form of voxel based analysis previously used for functional imaging, but modified to analyse structural MRI

images. All three tissue compartments were analysed (grey matter, white matter and CSF) and provided a comprehensive view of brain changes in patients with CTRD. The chapter also examines the clinical correlates of the brain changes in patients with CTRD in an attempt to define if these changes were acquired or pre-existent.

Chapter six examines the profile of cognitive change in patients with CTRD and recovered patients compared to controls from experiment two. Cognitive impairments may reflect the brain changes in those with CTRD. A further aim was to investigate if recovered patients had achieved full cognitive recovery. If there was residual impairment in the recovered group, this may reflect cerebral structural change. Thus, the results from the cognitive tests were correlated with grey matter in the CTRD group, predicting that episodic verbal memory would correlate with left hippocampus, and that measures of motor retardation would correlate with fronto-striatal regions.

Finally, chapter 7 summarises the findings of the experiments and puts forwards suggestions for further future investigations.

CHAPTER 2:

A REVIEW OF FUNCTIONAL IMAGING STUDIES IN PRIMARY DEPRESSION

CHAPTER 2: A REVIEW OF FUNCTIONAL IMAGING STUDIES IN DEPRESSION

2.1 An overview of the functional neuroanatomy of the limbic system

Broca in 1878 (Broca, 1878) first described the ring of tissue comprising the cingulate gyrus, anterior olfactory region, hippocampus and parahippocampal gyrus as *"le grand lobe limbique"* describing its function as olfactory. Lesion studies by Brown and Schlaepfer (Brown & Schlaepfer, 1888), and by Kluver and Bucy (Kluver & Bucy, 1938) (Kluver & Bucy, 1939) helped establish an emotional role for limbic structures. Ramon y Cajal (Ramon y Cajal, 1900) established the connection of other structures with the limbic lobe, including the amygdala, septal nuclei, hypothalamus, epithalamus, anterior thalamus and the basal ganglia, particularly the ventro-medial portions.

Papez (Papez, 1937) integrated the evidence from anatomical and clinical studies to propose a mechanism for emotion involving a limbic loop. He proposed that sensory information was relayed to the hippocampus via the primary sensory cortex. Via the fornix, information was passed to the mamillary bodies and then the hypothalamus, where (external) emotional expression, or affect, was initiated. Information then passed through the mamillo-thalamic tract to the thalamus and

then through the internal capsule to the cingulate gyrus where mood was consciously perceived as an internal state. The loop was completed by feedback to the hippocampus via the retrosplenic cortex.

Table 2.1

Brain regions regarded as part of the limbic system
Hippocampus
Parahippocampal gyrus
Mamillary bodies
Mamillothalamic tract
Thalamus
Cingulate gyrus
Orbito-frontal gyrus
Amygdala
Temporal lobe
Insular cortex
Ventral striatum

Interestingly, Papez regarded the cingulate cortex as the area that performed the integration between emotional response and (dorsolateral frontal) executive functions. Yakolev (Yakolev, 1948) independently proposed that the orbito-frontal cortex, amygdala, temporal lobe, insula and dorsal medial thalamus were important in mediating motivation and emotional expression. Finally, MacLean linked Papez' circuit with the

structures identified by Yakolev, referring to this network, for the first time, as the limbic system (McLean, 1952) (table 2.1).

Since then, the anatomical organisation of these components has revealed specific organisations within structures. For example, the anterior cingulate is recognised to have at least three functionally different subdivisions- a ventral affective, a cognitive and a motor division (Devinsky *et al*, 1995). The affective component includes Brodmanns' areas 33, 25, rostral 32 and 24 and have projections to lateral orbito-frontal cortex, limbic striatum and brainstem. These areas are activated during mood induction (George *et al*, 1995) and show increases during recovery from depression (Goodwin *et al*, 1993). The cognitive and motor divisions comprise Brodmanns' areas caudal 24 and 32 are activated with attentional and response selection tasks (Frith *et al*, 1991; Pardo *et al*, 1991), and have reduced activity in depression (Bench *et al*, 1992; Ring *et al*, 1994).

With increasing image resolution and spatial localisation of focal differences in brain activity, there has been a shift in the view of the neuroanatomy of depression- the limbic system is regarded as a number of component cerebral areas organised into discrete parallel loops with differing functions, which may be disturbed in depression. Alexander and colleagues (Alexander *et al*, 1986) suggest at least five segregated basal ganglia- thalamocortical loops, involving different parts of the frontal and cingulate cortex, striatum and thalamus. Three of these are

of particular relevance- the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate loops, the components of which are outlined in table 2.2. These have also been called the dorsal cognitive, ventral cognitive and affective-emotional circuits (Rauch & Savage, 1997), respectively, on the basis of function. The first is thought to play a role in complex cognitive processes including working memory and shifting mental sets, and the second in cognitive processes related to response inhibition for social or emotional material. The affective/ motivational loop, also heavily innervated by the amygdala, is involved in emotional or reward-based information processing (Rauch & Savage, 1997).

In summary, it is currently thought that the limbic system, together with subcortical brain regions;

> "mediate fundamental functions such as memory, emotion, motivation and mood. Limbic and subcortical systems also play a key neurobiological role in other aspects of human experience, such as substance abuse and reward systems."
>
> (from (Salloway *et al*, 1997)).

Table 2.2: The five segregated basal ganglia- thalamocortical loops

Loop (after Alexander et al 1986)	Functional description (after Rauch and Savage 1997)	Frontal cortical areas	Basal ganglia	Thalamic areas	Function
Dorsolateral prefrontal	Dorsal cognitive	Dorsal, lateral and anterior prefrontal	Dorsolateral caudate	ventral anterior, medial dorsal nuclei	working memory, establishing and shifting mental set
Lateral orbitofrontal	Ventral cognitive	Anterior and lateral orbitofrontal	Ventromedial caudate	Medial dorsal nuclei	response inhibition of social/ emotional material
Anterior cingulate	Affective/ motivational	Posteromedial orbitofrontal, anterior cingulate	Ventral striatum/ nucleus accumbens	Medial dorsal nuclei	Emotional/ reward- based information processing

It therefore follows that pathological mood states, such as depression, should involve dysfunction in these limbic and subcortical networks, specifically, that disturbances in the loops described above should produce specific cognitive and emotional change which map to discrete cortical areas showing change in activity.

2.2 Functional imaging of the human limbic system *in vivo*

The majority of recent functional (using PET or SPET) imaging studies compare regional blood flow or glucose metabolism either between different groups or between resting and active states. The central assumption (for pathological states) is that the normal condition of a tight coupling between regional metabolism and blood flow/ glucose metabolism holds during pathological states. If true, differences in local blood flow or glucose metabolism between groups or during activation should reflect the net difference in summed metabolic activity associated with terminal field synaptic transmission (Raichle, 1987; DiRocco *et al*, 1989). Further, because of functional segregation of brain regions, symptoms, mood or cognitive change should map to the specific regions involved in their production or regulation.

However, measuring metabolism is a second derivative of net regional neuronal activity. Within a region, there may be both inhibitory and excitatory influence which influence metabolism. Thus, it is not possible to attribute change in metabolism to a change in a single neurochemical systems are involved in depression, but, taken with

neuroanatomical studies, these studies provide indicators to candidate neurotransmitter systems.

2.3 Considerations in interpreting functional imaging studies

There are a number of factors that need consideration in interpreting functional imaging studies

First, many studies examine small samples of heterogeneous depressed patients. Clinical, aetiological and biological heterogeneity within and between samples increases variance and allows divergent or negative results dependent on the particular admixture of depressed patients. Regional metabolism may be expected to differ, for example, between a patient exhibiting prominent anxiety, psychomotor agitation and insomnia, from one showing avolition, motor retardation and hypersomnia. Thus samples have included mixtures of unipolar and bipolar patients, medicated and unmedicated patients, patients with/ without melancholic features, or psychotic symptoms, with/ without cognitive impairment, a mixture of in and out patients, patients with varying treatment responsiveness, and elderly patients with both late and early onset depression. Most of these dichotomies may be associated with particular patterns of perfusion or metabolism. Thus, it is important that samples are selected to have some degree of homogeneity over and above that of meeting criteria for a depressive episode, to limit the variance in the data, especially as the size of difference in regional activity is small.

Second, most studies have used region of interest (ROI) analysis methods. In this, the activity within a number of bounding boxes represents the activity from specific anatomical areas. The bounding boxes can be constructed using neuroanatomical templates (e.g. (Baxter *et al*, 1985; Ebert *et al*, 1991; Austin *et al*, 1992b)), or be an arbitrary shape (e.g. rectangle) distributed through the image (e.g. (Cohen *et al*, 1982; Cohen, 1988)). It assumes functional homogeneity within an ROI and that expected changes occur throughout the whole ROI or a majority part. Additionally, as ROIs are identified on *a priori* hypotheses, only a part of the data set (or image) is analysed. Further, the orientation of the brain during imaging, the positioning of ROIs and measurements are operator dependent. These considerations increase the variability in the data, and produce reduced spatial precision for any differences found.

Third, these small cross-sectional studies cannot allow the separation of state dependent from pre-existing trait or long term resultant changes. Detected differences may reflect, for example, the presence of cerebrovascular or thyroid disorder, gray matter atrophy or hypoplasia, or the effects of ageing, which may produce changes predisposing to, or resultant from depression. Longitudinal studies are required for this purpose.

2.4 The limbic system and mood in health

The normal physiology function of the limbic system can be examined by observing cerebral blood flow or metabolic changes with induced mood change in healthy volunteers. These studies find activation and attenuation of activity in different parts of the limbic network when mood is normally lowered. In a first study, Pardo and co-workers (Pardo *et al*, 1993) examined seven male and female volunteers whilst they remembered a sad event and found activation of bilateral inferior and orbitofrontal cortex. George et al (George *et al*, 1995) examined eleven healthy women during transient sadness, and found extensive limbic and paralimbic activation, specifically in right medial frontal gyrus, left dorsolateral prefrontal cortex, bilateral cingulate gyrus, basal ganglia, thalamus, fornix, left insula and left cerebellum. Mayberg and colleagues (Mayberg *et al*, 1995) examined healthy volunteers during maintained sadness. Activation was seen in insular and subgenual anterior cingulate regions, with reductions in prefrontal, inferior parietal, dorsal anterior and posterior cingulate. Baker et al (Baker *et al*, 1997) examined the effects of inducing a depressed mood analogous to retarded depression in nine controls. They found increases in lateral orbitofrontal and midbrain blood flow, with reductions in rostral medial frontal cortex. Thus, inducing a sad/ depressed mood in healthy controls initially produces both activation in orbitofrontal cortex, insular cortex and ventral parts of the anterior

cingulate, and attenuation in some prefrontal areas and parts of the anterior cingulate.

2.5 Resting state functional studies during primary depression

Table 2.3 reviews the SPET and PET studies of patients with primary depression. There is also considerable literature on functional imaging in secondary depression, which is not reviewed here, since, although there may be similarities in the findings, it is difficult to ultimately exclude the effects of the primary illness on activity.

Although the same limbic and subcortical areas are repeatedly found to be different in depression, there is considerable variance in the direction of change. The most consistent findings are of reduced flow or metabolism in bilateral dorsolateral prefrontal cortex and in the basal ganglia in unipolar depression. There is also some evidence for reduced temporal lobe perfusion, perhaps in treatment resistant patients and the elderly, as well as activity changes in the basal ganglia, amygdala and thalamus. Orbitofrontal perfusion appears to increase in depression, in contrast to dorsolateral prefrontal cortex. Most studies have had difficulty visualising or detecting change in medial temporal structures, partially contributed to by the limits in resolution of PET and SPET and because of the ROI method analysis. With VBA, increased perfusion has been detected in the amygdala that may, or may not normalise on recovery. Finally, the anterior cingulate, a structure of particular interest in affective disorders, is consistently

found to have changes in activity in depression. However, the direction of change ranges from increases, no change, to decreases in perfusion during depression. This may partially be attributable to the spatial blunting inherent in ROI analysis. The cingulate, like most other cerebral structures, is not functionally heterogeneous, having at least three subdivisions. It is possible that there are opposing changes occurring within a small area, producing a variable effect on ROI analysis. A number of hypotheses have been proposed incorporating the divergent changes in cingulate as well as orbitomedial frontal hyperperfusion (Ebert & Ebmeier, 1996; Mayberg, 1997; Drevets, 1998). It is interesting to note that these more spatially refined hypotheses of the neural substrate of depression have been enabled by voxel based analysis.

2.6 Clinical correlates of perfusion changes and changes with recovery.

Table 2.4 summarises the correlation of activity changes during depression with a number of clinical variables, and the changes that occur on recovery from depression using physical (ECT, light, sleep deprivation) and pharmacological methods.

Most studies have used the Hamilton Rating Scale for Depression (HRSD) to measure global severity of depression. Consistently, severity negatively correlates with lateral prefrontal metabolism or perfusion. Depression can be characterised along the neurotic/ endogenous continuum, the endogenous pattern corresponding to a melancholic

Table 2.3 A review of cerebral perfusion or metabolic changes found in primary depression

Group	Reference	Imaging technique	Analysis Technique	Sample size (Dep vs Con)	Ages (Dep vs Con)	Med status (free vs not)	Unipolar/ Bipolar	Blood flow/ glucose metabolism change in depressed group							Comments
								Cingulate	Ventral prefrontal cortex	Dorsolateral prefrontal cortex	Temporal cortex	Hippocam / parahip / amyg	Basal ganglia	Thalamus	
UCLA	Baxter et al, 1985	PET, ^{18}FDG	ROI	11/ 9	34.7/ 30.3	11/ 0	11/ 0	No effect	No effect	No effect	No effect	No effect	↓ caudate	No effect	
	Baxter et al, 1989	PET, ^{18}FDG	ROI	10/ 12		10/ 0	10/ 0	No effect	No effect	↓ bilateral	No effect	No effect	No effect	No effect	
NIMH	Buchbaum et al, 1986	PET, ^{18}FDG	ROI	20/ 24	39/ 31	20/ 0	4/ 16	Not measured	↓ bilateral ↑bilateral	in bipolars/ in unipolars	↓ bilat, R>L**	Not imaged	↓ in U/P	Not measured	**subset of patients Post (Post.1987)
	Cohen et al (1989)	PET, ^{18}FDG	ROI					No effect	No effect	↓ Right	↓ L middle	Not imaged	↓ Left		
	Cohen et al (1992)	PET, ^{18}FDG	ROI	7/ 38	44.9/ 36.2	7/ 0	SAD		↑ R medial orbital			Not imaged			
France	Martinot et al, 1990	PET, ^{18}FDG	ROI	10/ 10	49/ 38	3/ 7	3/ 7	Not measured	no effect	↓ Left	no effect	not measured	no effect	not measured	
Univ. Erlangen	Ebert et al, 1991	SPET, ^{99m}TcHMPAO	ROI	10/ 8	38.9/ 41.5	10/ 0	Melancholic dep	↑ bilat lower cing^	↑ bilat orbito-frontal^	↓ Left	↑ bilat inferior^	↑ R hipp/ para/ amyg^	No effect	No effect	^ responders to sleep deprivation only
MRC Cyclotron unit	Bench et al, 1992	PET, $H_2{}^{15}O$	VBA	33/ 23	56.8/ 63.4	14/ 19	30/ 3	↓ L. anterior	↓ Left	↓ Left	No effect	Not imaged	No effect	No effect	Medication effect not detected
MRC BMU	Austin et al, 1992b	SPET, ^{99m}TcHMPAO	ROI	40/ 20	45.8/ 47.2	25/ 15	40/ 0	No effect	Not imaged	↓ bilateral	↓ bilateral anterior temporal	Not imaged	↓ bilateral	↓ right	Medication assoc with ↓ uptake
	Curran et al, 1993	SPET, ^{99m}TcHMPAO	ROI	20/ 30	70/ 67.1	9/ 11	20/ 0	↓ bilateral*	Not imaged	↓ bilateral*	↓ bilateral middle temporal*	Not imaged	↓ bilateral caudate*	↓ bilateral*	*males only

Table 2.3 A review of cerebral perfusion or metabolic changes found in primary depression

Group	Reference	Imaging technique	Analysis Technique	Sample size (Dep vs Con)	Ages (Dep vs Con)	Med status (free vs not)	Unipolar/ Bipolar	Blood flow/ glucose metabolism change in depressed group							Comments
								Cingulate	Ventral prefrontal cortex	Dorsolateral prefrontal cortex	Temporal cortex	Hippocam / parahip / amyg	Basal ganglia	Thalamus	
PET Cyclotron Unit, Brussels	Biver et al (1994)	PET, ^{18}FDG	ROI	12/ 12	37.6/ 31.1	12/ 0	12/ 0	No effect	↑ orbito-frontal	↓ bilateral	No effect	Not imaged	No effect	No effect	
UCLA2	Lesser et al, 1994	SPET, ^{99m}TcHMPAO	ROI	39/ 20	60.9/ 69.1	39/ 0	39/ 0	No effect	↓ bilat orbito-frontal	↓ Right	↓ R superior	Not measured	Not measured	Not measured	
Pittsburg, Penn	Mentis et al (1995)	PET, ^{18}FDG		11/ 12	?	11/ 0	11/ 0	?	↑ orbital/ lateral	no effect		↓ Left amygdala		↓ Left	
	Drevets et al, 1992	PET, $H_2{}^{15}O$	VBA	13/ 33	36.2/ 30.1	13/ 0	13/ 0	↑ pregenual anterior	↑ bilat lat orbital	no effect	↓ R medial	↑ amygdala (L>R)	↓ Bilat	↑ Left	
	Drevets et al (1995)	PET, ^{18}FDG		31/ 17		31/ 0	31/ 0	↓ subgenual anterior	↑ bilat lat & med orb	↓ Left	?	↑ amygdala (L>R)	no effect	↑ ?	
San Antonio, Texas	Mayberg et al, 1994	SPET, ^{99m}TcHMPAO	ROI	13/ 11	42/ 35	0/ 13	13/ 0	↓ anterior	not examined	↓ bilateral	↓ bilateral	not examined	↓ bilateral	↓ bilateral	
	Mayberg et al, 1997	PET, ^{18}FDG	VBA												
Sendai, Japan	Ito et al (1996)	SPET, ^{99m}TcHMPAO	VBA	17/ 9	66.6/ 65.7	0/ 17	11/ 6	↓ right anterior	no effect	↓ bilateral	↓ L sup, ant and insula	no effect	no effect	no effect	unipolars and bipolars similar
Herzog, Israel	Bonne et al, 1996	SPET, ^{99m}TcHMPAO	ROI	20/ 21	59/ 57.4	20/ 0	11/ 9	no effect	no effect	no effect	↓ L superior	no effect	no effect	no effect	treatment resistant, no uni/ bi diff

Table 2.4: A review of the functional correlates of perfusion and metabolic change in primary depression

			Correlation with blood flow/ metabolic activity					
Group	Reference	Hospitalised	Depression severity	Endogenous/ Neurotic	Cognitive impairment	Motor retardation	Medication (on/ off)	Changes with recovery
UCLA	Baxter et al, 1985	?	17- 25 (21 point HDRS)	?	?	?		4/ 11 U/ Ps rescanned: ↑ L caudate
NIMH	Buchbaum et al, 1986	?	5.7 +/- 3.6 (BHR): +ve correlation with frontal					
	Wu et al (1992)	15 Outpatients	>17 (21 HRSD)					Before Rx: ↑ anterior cingulate and amygdala in PSD responders After Rx: ↓ in cingulate only in PSD responders only
	Cohen et al (1992)	7 out-patients	17- 28 (21 HDRS) -ve with L medial frontal					↑ R posterior frontal with response to light Rx
France	Martinot et al, 1990	In-patients	56.6 +/-6 (26 HRSD): no correlation with DLPFC	-32.3 +/-8 (Newcastle)- endogenous pattern				(10 pts) ↑ L prefrontal on recovery
Univ. Erlangen	Ebert et al, 1991	?	27. 6 +/- 7.8					Before: ↓ L anterolateral prefrontal ↑ bilateral fronto-orbital, low anterior cingultae, R hippocampus, bilateral inferotemporal After TSD: blood flow normalised in these areas
MRC Cyclotron unit	Bench et al, 1992	?	25 +/- 4.1 (17 HDRS): ?		10/ 10 (MMSE <26 vs >28): ↓ L medial prefrontal ↑ cerebellar vermis		19/ 14: No effect	
	Bench et al (1993)(sample includes Bench et al, 1992)	?	25.2 +/- 4.3 (17 HDRS) Mood and retardation factor: negative correlation with L DLPFC and L angular	Anxiety factor: +ve correlation with posterior cingulate and inferior parietal	Cognitive performance factor: +ve with L medial prefrontal R thalamus, R superior temporal, bilateral posterior cingulate	Mood and retardation factor: -ve correlation with L DLPFC and L angular	20/ 20: No effect	
	Dolan et al (1994)	?	25 +/- 4.2 (17 HDRS): ?	Attentional factor: +ve with medial frontal gyrus inferior posterior central gyrus, middle temporal and angular gyrus	Memory factor: +ve with anterior medial prefrontal including anterior cingulate, and retrosplenic, precuneus and post cingulate	?	No effect	
	Bench et al (1995)- 25 of sample in Bench et al (1993)	?	7.6 +/- 5.1 (17 HDRS)		Memory factor: persistant +ve correlation with antero-medial prefrontal including anterior cingulate			↑ L DLPFC, bilateral medial prefrontal, high anterior cingulate, (posterior to angular gyrus only in those with consistant medication)

Table 2.4: A review of the functional correlates of perfusion and metabolic change in primary depression

			Correlation with blood flow/ metabolic activity					
Group	Reference	Hospitalised	Depression severity	Endog/ Neur	Cognitive impairment	Motor retardation	Medication (on/ off)	Changes with recovery
MRC BMU	Austin et al, 1992b	In-patients	22. 4 +/-5.6 (17 HRSD) -ve with R dorsolateral prefrontal, R putamen	5.0 +/-3.2 +ve with R posterior and anterior cingulate, L DLPFC		↑ motor retardation correlated with ↑ in R posterior cingulate and R basal ganglia		
	Goodwin et al, 1993	28 patient follow-up	3.5 on recovery (17 HRSD)	for lower frontal areas- ↓ in endogenous ↑ in neurotic on recovery				↑ bilateral basal ganglia and inferior anterior cingulate, R posterior cingulate and thalamus
	Curran et al, 1993	20 in-patients	23.5 +/- 7.9(17 HRSD)	6.5 +/- 2.6		↑ motor retardation correlated with ↓ in bilateral prefrontal, R anterior and posterior cingulate		
	Scott et al, 1994	15 inpatients						Acute effect of ECT- ↓ inferior anterior cingulate. Change correlated with HRSD
PET Cyclotron Unit, Brussels	Biver et al (1994)	12 inpatients	31 +/-7 (24 HRSD): no correlation	6 endog/ 6 other: no difference				
	Mentis et al (1995)							
Pittsburg, Penn	Drevets et al, 1992	?	27.3 +/- 4.6 (21 HRSD): +ve correlation with amygdala, -ve correlation L prefrontal cortex	"melancholic type", recurrent	No corr. of "anxiety" and amygdala/ L prefrontal cortex	?	?	Activity normalised in L prefrontal. persistant ↑ in amygdala
	Drevets et al (1995)							
San Antonio, Texas	Mayberg et al, 1994	In-patients	22 +/-5 (HRSD): no correlation	18 =/-6 HAS	All patients >28 MMSE	Motor slowing scale -ve correlation with limbic (frontal, temporal) and prefrontal cortex.		
	Mayberg et al, 1997							
Herzog, Israel	Bonne et al, 1996	In-patients	25.9 +/- 5.2 (21 HDRS): -ve with medial temporal, parietal, lateral frontal					
	Vasile et al (1997)	10 SAD patients	~31 (SIGH-SAD): ?					↑ in light treatment responders (5) only- frontal, anterior cingulate, thalamus
	Volk et al (1997)	15 patients	21.1 (21 HRSD): ?	Melancholic type				Before Rx: ↑ R orbitofrontal/ basal cingulate in PSD responders

type of depression. The few studies that have examined this, found an endogenous pattern on the Newcastle scale (Carney *et al*, 1965) was associated with a higher anterior cingulate perfusion (Austin *et al*, 1992b) in middle aged patients, but with a lower perfusion in lower frontal areas in the elderly (Curran *et al*, 1993). Motor retardation is regarded by some authors as a key symptom of depression (Widlöcher, 1983; Parker *et al*, 1993)- activity in prefrontal cortex, cingulate and striatum appear to correlate with clinically and objectively measured motor retardation. Finally, cognitive impairment, which is often seen in hospitalised depressed patients, correlated with anterior medial frontal areas, and temporal areas.

One night of total sleep deprivation (TSD) can improve depressive symptoms in about 60% of patients (Wu & Bunney, 1990). Consistently, studies have shown that patients who respond to TSD initially have high orbito-cingulate perfusion (Ebert *et al*, 1991; Wu *et al*, 1992; Wu *et al*, 1994; Ebert *et al*, 1994b) which decreased on recovery, and that the improvement in depression after TSD correlated with reductions in orbitofrontal perfusion (Volk *et al*, 1993). It is possible that orbito-cingulate hyperperfusion characterised TSD responders only (Wu *et al*, 1992; Volk *et al*, 1993). In contrast, with pharmacotherapy a number of research groups have found some degree of reversibility in perfusion deficits in dorsolateral and medial prefrontal cortex as well as anterior cingulate (Goodwin *et al*, 1993; Dolan & Goodwin, 1995) in

patients matched for medication status, as well as in frontal metabolism in patients not matched for medication (Baxter *et al*, 1989; Hurwitz *et al*, 1990; Martinot *et al*, 1990) although there may not have been complete restitution in frontal and temporal areas (Goodwin *et al*, 1993). The short-term (45 minutes after treatment) effects of ECT (Scott *et al*, 1994) include reduction in anterior and inferior cingulate, whereas the longer term effect (Lerer *et al*, 1994) was for anterior and posterior cingulate perfusion increases in ECT responders.

In summary, diverse results have been obtained for activity changes on recovery, particularly anterior cingulate. This may be since different areas of the anterior cingulate were sampled, with hyperperfusion seen in more ventral parts and hypo-perfusion in dorsal parts during depression (Ebert & Ebmeier, 1996), or that sample groups had differing symptom profiles which have been found to be associated with different cingulate perfusion patterns (Austin *et al*, 1992b; Goodwin *et al*, 1993). Alternatively, Mayberg (Mayberg, 1997) has suggested that perfusion in rostral anterior cingulate (Brodmann area 24) predicts treatment response. Patients who respond have pre-treatment hyper-perfusion, with non-responders being hypo-perfused.

Also, not all areas showing perfusion change during depression return to normal on recovery (e.g. basal ganglia, temporal and frontal cortex), suggesting that there may be trait differences in depressed patients. This, together with neuropsychological changes that occur with

depression, give support to the notion of depression as a "fronto-subcortical" or "fronto-striatal" dementia (Robbins *et al*, 1992).

2.7 Summary

The pattern of cerebral perfusion and metabolic change in primary depression is complex, but involves a network of limbic and subcortical structures, specifically orbito-frontal, medial frontal and dorsolateral prefrontal cortex, several anterior cingulate regions, the striatum, amygdala and temporal cortex. The pattern of change in discrete areas may be a correlate of overall depression severity, symptom profile, cognitive impairment or motor slowing.

The prominent involvement of the striatum, anterior cingulate and prefrontal areas strongly suggest the contribution of the dopaminergic system in the pathophysiology of depression, these areas having the greatest density of dopaminergic innervation (Graybiel, 1990). This provides some of the rationale in investigating striatal dopamine D2/3 receptor availability in depression (Chapter 3).

Not all perfusion changes in depression appear to reverse on recovery, suggesting a trait effect, possibly secondary to structural differences. Chapters 4, 5 and 6 lay out an investigation of MRI changes in patients with chronic treatment resistant depression, a group of patients who, it will be argued, may have a greater likelihood of exhibiting structural brain changes.

CHAPTER 3 : CLINICAL AND PSYCHOMETRIC CORRELATES OF DOPAMINE D_2 BINDING IN DEPRESSION

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CHAPTER 3 : CLINICAL AND PSYCHOMETRIC CORRELATES OF DOPAMINE D_2 BINDING IN DEPRESSION

3.0 ABSTRACT

Single photon emission tomography (SPET) with the dopamine $D_{2/3}$ ligand ^{123}I-IBZM gives a semi-quantitative estimate of receptor availability. We predicted evidence of reduced function, i.e. increased binding, particularly in more motor retarded patients.

15 patients with major depressive illness and 15 healthy, age and sex matched volunteers were examined with a clinical and neuropsychological test battery and high resolution IBZM-SPET. Estimates for specific binding were computed by averaging striatum to whole slice uptake ratios over 8-10 scans acquired from 70 minutes after tracer injection.

IBZM binding was higher in the right striatum in depressed patients compared to controls, with no difference in left striatal binding ratios. There were significant correlations between IBZM binding in left and right striatum, and measures of reaction time and verbal fluency. Increased IBZM binding in striatum probably reflects reduced dopamine function, whether due to reduced tonic release of dopamine, or secondary receptors up-regulation. The difference in the depressed group may be trait or state related, reversible or irreversible. This can only be addressed by longitudinal studies.

The possible confounding effect of medication requires further exploration.

The variation in specific binding in healthy controls was examined. Women exhibited increased binding compared to men, an effect size of 0.8. Specific personality dimensions were strongly correlated with IBZM binding in controls, suggesting a trait effect on binding, adding to the weight of evidence implicating the basal ganglia in complex behaviours.

3.1 INTRODUCTION

3.1.1 Limbic dopamine and depression

It will be evident from the preceding section that the basal ganglia, anterior cingulate and prefrontal cortex are key components of the limbic system showing changes during normal mood change, pathological depression and on recovery using associated with pharmacotherapy (Goodwin *et al*, 1993), ECT (Lerer *et al*, 1994; Scott *et al*, 1994), sleep deprivation (Ebert *et al*, 1991; Wu *et al*, 1992; Volk *et al*, 1993; Wu *et al*, 1994; Ebert *et al*, 1994a) . No single neurotransmitter can fully explain the range of mood, motor, cognitive and somatic symptom found in depression. However, since dopaminergic neurones heavily innervate many of the cerebral areas involved in depression, it is likely that dopamine does play a role in the neurochemistry of depression. This potentially challenges conventional theory that dopamine transmission is related to schizophrenia, with serotonin and noradrenalin being related to depression..

The mesolimbic dopaminergic neurones are of importance here, originating in the ventral tegmental area (VTA) which specifically projects to orbito/ ventral prefrontal cortex, anterior cingulate and ventral striatum (Graybiel, 1990). They have been implicated in depressive behaviour in humans and in animal models of reward seeking behaviour (Fibiger, 1993). In fact, animal models of depression suggest the mesolimbic system, including the ventral striatum/ nucleus accumbens is involved in the pathophysiology of depression (Willner, 1995). Although dopaminergic innervation is

more widespread in humans, the greatest projections are to anterior cingulate and motor cortex (Berger *et al*, 1991). Consequently, it is not surprising that apomorphine, a dopamine agonist, has been found to increase medial prefrontal, particularly anterior cingulate perfusion, in normal subjects using PET (Grasby *et al*, 1993; Kapur *et al*, 1994).

Further evidence of dopaminergic involvement in depression comes from patients with Parkinson's disease (PD) who exhibit an associated (anterior cingulate) dopaminergic depletion and have exhibit high rates of depression (Cummings, 1992). Depressed patients with PD had reductions in perfusion in antero-medial prefrontal cortex and anterior cingulate compared to non-depressed PD patients and controls (Ring *et al*, 1994).

Additionally, many antidepressants, such as tricyclics, monoamine oxidase inhibitors, nomifensine, bupropion and electro-convulsive treatment, exhibit direct or indirect dopamine enhancing effects, although these actions are not ordinarily postulated to be the primary mechanism of action. Moreover, some agents with mainly dopaminergic effects, amphetamine, pirebidil and bromocriptine, may have antidepressant action (Diehl & Gershon, 1992). Additionally, a reduced turnover of dopamine, determined by the measurement of homovanillic acid in cerebrospinal fluid, has been demonstrated in depressed patients, particularly if motor retardation is present. (van Praag & Korf, 1975); (Jimerson, 1987).

Despite the above evidence, it is not altogether clear how dopaminergic activity interacts with the network of limbic structures found to

have altered activity during depression. One hypothesis is that reduced dopaminergic neurotransmission may result in disinhibition of the amygdala leading to activation of other limbic structures "in the loop" and inhibition of the basal ganglia (Ebmeier & Ebert, 1996). A first step, therefore, is to establish what happens with the dopaminergic system, *in vivo* during depression.

Three single photon emission tomography (SPET) studies have examined dopamine function more directly in depression, by using ^{123}I-IBZM (^{123}I-3-iodo- methoxybenzamide), a benzamide derivative with high $D_{2/3}$ receptor selectivity (Verhoeff *et al*, 1992), but moderate affinity to dopamine receptors. Its specific binding, therefore, reflects receptor binding and any partial displacement by endogenous ligand (Laruelle *et al*, 1995). Specific IBZM binding in the striatal regions of interest (ROIs) has been found to be increased in the depressed group compared with controls, suggesting either a reduction in competition from endogenous dopamine or an up-regulation or increased affinity of IBZM to $D_{2/3}$ receptors (D'haenen & Bossuyt, 1994). A second study could not confirm this effect for all depressed patients examined, but found IBZM binding to be specifically higher in patients with psychomotor retardation (Ebert *et al*, 1996). IBZM binding was reduced after successful pharmacological treatment and a concomitant improvement in motor retardation (Ebert *et al*, 1996). The same pattern of change in IBZM binding was found in depressed patients with a successful antidepressant response to total sleep deprivation (Ebert *et al*, 1994a).

3.1.2 Correlates of variation in normal striatal dopamine function

In humans, PET imaging studies have found considerable variation in basal ganglia D2 receptor density in normal healthy subjects, a finding confirmed by post-mortem studies (Farde *et al*, 1995). The correlates of this normal variation are yet to be established. Although it has not been convincingly demonstrated that striatal dopamine $D_{2/3}$ receptors in humans are causally related to persistent behaviour patterns or personality traits, animal studies suggest that the basal ganglia, particularly the ventral striatum and nucleus accumbens, is involved in behaviours related to reward and motivation (Salomone, 1992), (Robbins & Everitt, 1996). Dopamine D2 receptor density is greatest in the caudate/ putamen and nucleus accumbens/ ventral striatum as well as on dopaminergic cell bodies within the substanstia nigra and VTA. D2 receptors are also present on cholinergic interneurones and thus may be involved in reward -based learning (Mello & Villares, 1997). VTA dopaminergic neurones fire in relation to reward stimuli and reward conditioned and direct stimulation of the VTA in rodents inhibits cingulate neurones either through D2 receptors directly or by dopaminergic stimulation of cortical inhibitory cells (Finch, 1993). D3 receptors are particularly found in the nucleus accumbens/ ventral striatum as well as hippocampus and mammilary nuclei, forming part of a system with several diverse inputs from several limbic structures, suggesting a role for them in cognitive and emotional functions (Palermo-Neto, 1997)..

Neurones in the ventral striatum discharge in relation to the reward properties of unconditional stimuli and may be involved in the motivational aspects of behaviour (Schultz *et al*, 1992). Laboratory rats, for example, dichotomised on the basis of behaviour in novel environments into high and low responders, differ in their predisposition to drug taking, in their sensitivity to the reinforcing properties of food and in the basal activity of the dopamine system in the nucleus accumbens (Dellu *et al*, 1996). Thus, these structures may form part of the "neural mechanism by which motivation gets translated into action" (Robbins & Everitt, 1996).

Two imaging studies have found a relationship between personality traits and striatal dopamine receptor availability. Gray et al (Gray *et al*, 1994) found strong negative correlations between both left and right basal ganglia IBZM binding and Psychoticism. Farde et al (Farde *et al*, 1997), in a quantitative PET study using [^{11}C] raclopride found a strong negative correlation between scores of "detachment" and D2 receptor density in the putamen, specifically excluding the D3 dopamine receptor rich ventral striatum. The detachment scale is one of fifteen from the self-reported "Karolinska Scales of Personality", a personality inventory thought to measure biologically based dimensions, with no apparent correlation with any of Eysenck's dimensions (Schalling *et al*, 1987). However, there is descriptive similarity between these dimensions. High "detachment" appears to characterise subjects who avoid involvement with other people, and avoid giving and taking

confidences (Schalling *et al*, 1987), high Psychoticism scorers characterise people who are cold, impersonal, unempathic and tough-minded (Eysenck & Eysenck, 1975) and low scorers of reward dependence are characterised by being socially detached, avoiding personal confidences and preferring to be independent (Cloninger, 1987).

3.1.3 Aims of study

Depressed patients: Ebert et al (Ebert *et al*, 1996) dichotomised patients by the presence or absence of retardation, but did not specifically investigate the cross-sectional relationship between IBZM binding in depression and more objective measures of psychomotor speed, reflecting varying degrees of psychomotor retardation. This study was designed to compare IBZM binding in the striatum between a depressed group and matched healthy volunteers, predicting a significant excess of binding in the patients, which was likely to be correlated with objective measures of motor and cognitive speed.

Controls: One of the tasks in investigating the biological basis of personality is to establish the external or criterion validity of personality dimensions. The external validity of Psychoticism In the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975), has attracted the greatest degree of criticism (Block, 1977) as it has a non-normal distribution in control populations, and since it was initially thought to measure psychosis-proneness. External validity is also limited for newer personality models. The Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987), is based on a

model of personality proposing that the dimensions of harm avoidance, reward dependence and novelty seeking reflect genetically heritable trait behaviours dependent on the function of central serotonin, noradrenalin and dopamine, respectively. Although an extension of the evidence from animal studies, direct confirmation from human control population studies is lacking. Personality inventories not based on biological models, such as the currently popular NEO-5 inventory (Costa & McCrae, 1992) also do not have established external validity for their constituent dimensions.

Thus, this study was designed to replicate the findings of Gray et al (Gray *et al*, 1994) as well as examine correlations between specific striatal binding and personality dimensions from the TPQ and NEO-5 inventories. In theory, striatal IBZM binding should correlate with scores of novelty seeking in the TPQ. However, since a comparison of inventories (Zuckerman & Cloninger, 1996) suggests that reward dependence, and not novelty seeking, has a closer correlation with Psychoticism on the EPQ, reward dependence scores may correlate with specific IBZM binding. There was no a priori hypothesis about which dimension(s) from the NEO-5 would correlate with IBZM activity. However, since scores of agreeableness and conscientiousness in the NEO-5 weight the most towards scores of Psychoticism (McCrae & Costa, 1985) , it may be that striatal IBZM binding would correlate positively with either one.

3.2 METHODS

3.2.1 Subjects

The design of the study was approved by the local research ethics committee and the appropriate committee at the Department of Health (ARSAC). Written informed consent was obtained from all participating subjects. 15 in-patients (9 males, 6 females) from the Royal Edinburgh Hospital fulfilling DSM-III-R criteria (American Psychiatric Association, 1987) for a current major depressive episode with or without melancholic or mood-congruent psychotic features and fifteen healthy volunteers were entered into the study. The groups were matched for age, sex, and premorbid IQ.

Two of the depressed patients had a bipolar affective disorder. Four patients were free of all medication at the time of scanning, seven were free of antidepressant medication. Eight patients were on antidepressant medication (including lithium) only, three on benzodiazepines only (appendix 3.1). The remaining four were free of all medication at time of scanning. For at least three months prior to the investigation, patients had not received any medication acting directly on the dopamine system, such as neuroleptics. None had received depot neuroleptics previously. The severity of symptoms was assessed using the 17-item Hamilton Depression Rating Scale (Hamilton, 1960), and the patient's position on the neurotic / endogenous continuum was measured by the Newcastle scale (Carney *et al*, 1965).

Controls were screened for the presence of psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978), and were free of any medication. Both patients and controls were required to be in good physical health, particularly with no evidence of alcohol or substance misuse, significant neurological illnesses or brain trauma. All patients were right-handed, two of the controls were predominantly left-handed.

3.2.2 Imaging Protocol

Subjects were imaged using a single slice twelve-detector head scanner, with an in-slice and z-axis resolution of approximately 8.5mm (full width half maximum), and a sensitivity of 520 counts per second in a head-sized phantom filled with 1kBq/ml (Ebmeier *et al*, 1991).

All subjects took oral doses of potassium iodate to ensure thyroid saturation with iodine and to prevent its excess exposure to radiation, 170mg each on the night before and the morning of the scan, 85mg the day after the scan. All scans were performed in the morning. An indwelling catheter was inserted into an arm vein 15-30 minutes before the injection of 185 MBq of ^{123}I-IBZM over 30 seconds. During and for 5 minutes after injection, patients were required to lie still and silent wearing eye patches with ears unplugged, with background noise kept to a minimum. The subject's head was then placed in a moulded headrest, positioned with the help of two crossed light beams, and fixed with two pressure pads over the zygomatic arches.

Slices were acquired parallel to the orbito-meatal line (OML). During the first hour, a full scan of the brain was carried out, followed by a short sequence of scans around the level of the basal ganglia, allowing the operator to choose the slice position with maximum activity from the striatum, approximately 4 cm above the OML. Single slices were then acquired at this level in a time series from 80 minutes to 140 minutes post injection. IBZM studies in healthy volunteers have found specific activity to be at a steady state during this period (Verhoeff *et al*, 1992).

3.2.3 Image Analysis

Analyses of the scans were carried out by a physics technician who was blind to the clinical details. Regions of interest (ROIs) were drawn in advance from a standard brain atlas (Talairach *et al*, 1988), outlining left and right frontal cortex, striata and brain slice hemispheres. The complete templates were linearly re-positioned, re-sized and deformed, so that the outlines of the hemisphere ROIs fit over the cortical rim, defined by the 20% isocontour line (Ebmeier *et al*, 1991). The striatal ROIs were then manually re-positioned and centred over maximal striatal activity if necessary, but were not re-sized. Once the template position had been determined for each subject, no further adjustment of the template was permitted. Following the previous studies, a regional uptake ratio was calculated as the ratio of the striatal ROI activity to reference ROI. With this approach, striatal activity (presumed to represent specific + non-specific binding + free ligand) is compared to a background

region (non-specific binding + free ligand), providing a functional index of specific binding of IBZM to $D_{2/3}$ receptors. The choice of reference region is critical, as different reference regions may affect results (Ebmeier & Ebert, 1996), especially if it includes the basal ganglia. For example, the use of whole slice activity as a reference region may reduce the power of comparison by including areas with high specific binding in both numerator and denominator (Ebert & Ebmeier, 1996). On the other hand, using a smaller reference region may increase variability of the uptake ratios (Ebmeier *et al*, 1991) Finally, it has to be considered that non-specific binding may not be the same for different subjects and thus may confound group comparisons (Laruelle *et al*, 1995). For comparison, we chose two reference regions - whole slice and frontal cortex. Regional uptake ratios were calculated for each scan in the time series and were then averaged across 8 - 10 scans to remove noise. The mean time of the scans was well matched for the two groups (118 (SD=5) minutes in controls vs. 121 (SD=8) minutes in patients post-injection).

3.2.4 Neuropsychological testing

All subjects were tested under standardised conditions. On the morning prior to the scan subjects performed the National Adult Reading Test revised (Nelson & Willison, 1991) to measure premorbid IQ, the auditory verbal learning test (AVLT; (Rey, 1964); (Lezak, 1983)), the Digit Symbol Substitution Test (DSST; (Wechsler, 1981)), Trail-making A and B from the Army Individual Test Battery

(Army Individual Test Battery, 1944), the F.A.S.-Verbal Fluency test (Borkowski *et al*, 1967), and the reaction time tasks from the CANTAB. computerised psychometric testing battery (Sahakian & Owen, 1992), which allow for a separate determination of the response initiation and movement times. This battery was chosen as the tests were thought to measure differing aspects of motor and cognitive speed.

On the morning of the scan, subjects performed a maximum voluntary contraction (MVC) task. Each subject was asked to squeeze a dynamometer as hard as they could, and the average of three trials with the right hand was used for analysis. This follows the work of Cohen et al. (Cohen *et al*, 1982) who demonstrated that deficits in motor performance in depressed patients was proportionate to their level of depression, and also Moffoot et al (Moffoot *et al*, 1994) who found a reduction in performance in melancholically depressed patients sensitive to diurnal variations in mood. It has been suggested that a reduced performance may reflect a generalised reduction in central motivational state or in effort. Subjects also completed the Befindlichskeitskala (BFS; (von Zerssen *et al*, 1974)), an adjective check list of 28 word-pairs reflecting their present state of mind. The scale has two sub-scores, one for the degree of fatigue experienced, the other for the degree of depression felt. Finally, the Alderly Park State Anxiety Questionnaire (APSAQ; (Walker, 1990)) was used to assess the subject's level of state anxiety just after the injection of the ligand.

Eleven of the healthy volunteers completed the Eysenck Personality Questionnaire to determine scores of extroversion, neuroticism and psychoticism (Eysenck & Eysenck, 1975). All the volunteers were posted the Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987) and the NEO-5 (Costa & McCrae, 1992) questionnaires at least six months after having been scanned, after preliminary investigations of the associations with the EPQ. Ten subjects returned completed TPQ and NEO-5 questionnaires.

3.2.5 Statistics

Data were analysed with SPSS (version 4) for the Apple Macintosh. Since clear hypotheses existed for the direction of group differences, comparisons were made by one-tailed Mann-Whitney U-Tests. For correlations between Hamilton scores, psychometric tests and striatal tracer uptake, Spearman's one-tailed correlation coefficients were computed. Non-parametric tests were used consistently, because some variables were not normally distributed. Exploratory correlations are descriptive, or at best, hypothesis generating. Univariate 95% confidence intervals (CI) were computed for correlation coefficients to provide a more practical description of the effect. However, correlations of measures of psychomotor retardation with striatal IBZM uptake were planned, hypothesis testing, and therefore did not require correction for multiple comparisons.

3.3 RESULTS

3.3.1. General

Patients and controls were well matched for age and sex (table 3.1, appendix 3.1). The average 17-item Hamilton score was 23.5 (SD = 7.6, range = 8 to 45) in the depressed group, the mean Newcastle score 6.9 (SD = 2.28, range = 2 to 11). Four of the 15 patients had obvious retardation (Hamilton score of 2+). One patient was not able to co-operate with the whole scanning sequence, and was, therefore, not included in the analysis of imaging data.

3.3.2. Psychometric testing

As expected, patients reported more depression and fatigue than controls (Table 3.1, appendix 3.2 and 3.3). Patients were weaker than controls in the hand grip task, were slower in reaction movement time and tended to be slower for total reaction time, response initiation time and tended to have poorer verbal fluency. There were no differences between patients and controls for state anxiety and for other neuropsychological tests.

3.3.3. IBZM binding and diagnosis

Depressed patients had higher right striatal activity than controls (figure 3.1 and 3.2, table 3.2, appendix 3.1), using whole slice as a reference region (mean= 1.68 (SD= 0.08) *v.* 1.62 (0.07), Cohen's d = 0.8, Mann-Whitney U-Test: Z= 1.8, p=0.03) (Figure 3.1). Using whole slice activity as reference, there was no significant effect on the left side

Table 3.1: Clinical and neuropsychological differences between fifteen depressed patients and fifteen controls.

Variable	Depressed (n=14)	Controls (n=15)	Mann-Whitney U-test (p)
Age (Years)	45 (14)	41 (10)	0.54*
Sex (M\F)	9\6	9\6	
NART IQ	112 (10)	116 (7)	0.24*
Education (Years)	13 (3)	15 (2)	0.07*
APSAQ	9 (8)	5 (4)	0.24
BFS Total	26 (14)	9 (8)	**0.002**
BFS Mood	6 (5)	1 (2)	**0.01**
BFS Fatigue	6 (5)	2 (3)	**0.004**
Isometric contraction (kg)	34 (15)	45 (14)	**0.03**
Total reaction time (msec)	684 (227)	571 (63)	0.06
Response initiation time (msec)	524 (168)	449 (47)	0.09
Movement time (msec)	488 (353)	330 (58)	**0.05**
Digit symbol substitution test	10 (2)	11 (2)	0.15
Trails A (seconds)	32 (7)	32 (9)	0.49
Trails B (seconds)	90 (108)	54 (17)	0.25
Verbal Fluency (words/ 3 mins)	39 (20)	48 (10)	0.09
AVLT total (5 trials)	49 (15)	55 (8)	0.24
Delayed recall (no. words)	10 (4)	12 (3)	0.31
Delayed recognition (no. words)	12 (6)	13 (3)	0.29

Figure 3.1 Mean striatal (basal ganglia) to whole slice activity ratios in depressed patients and controls.

Error bars indicate +/- 1 SD.

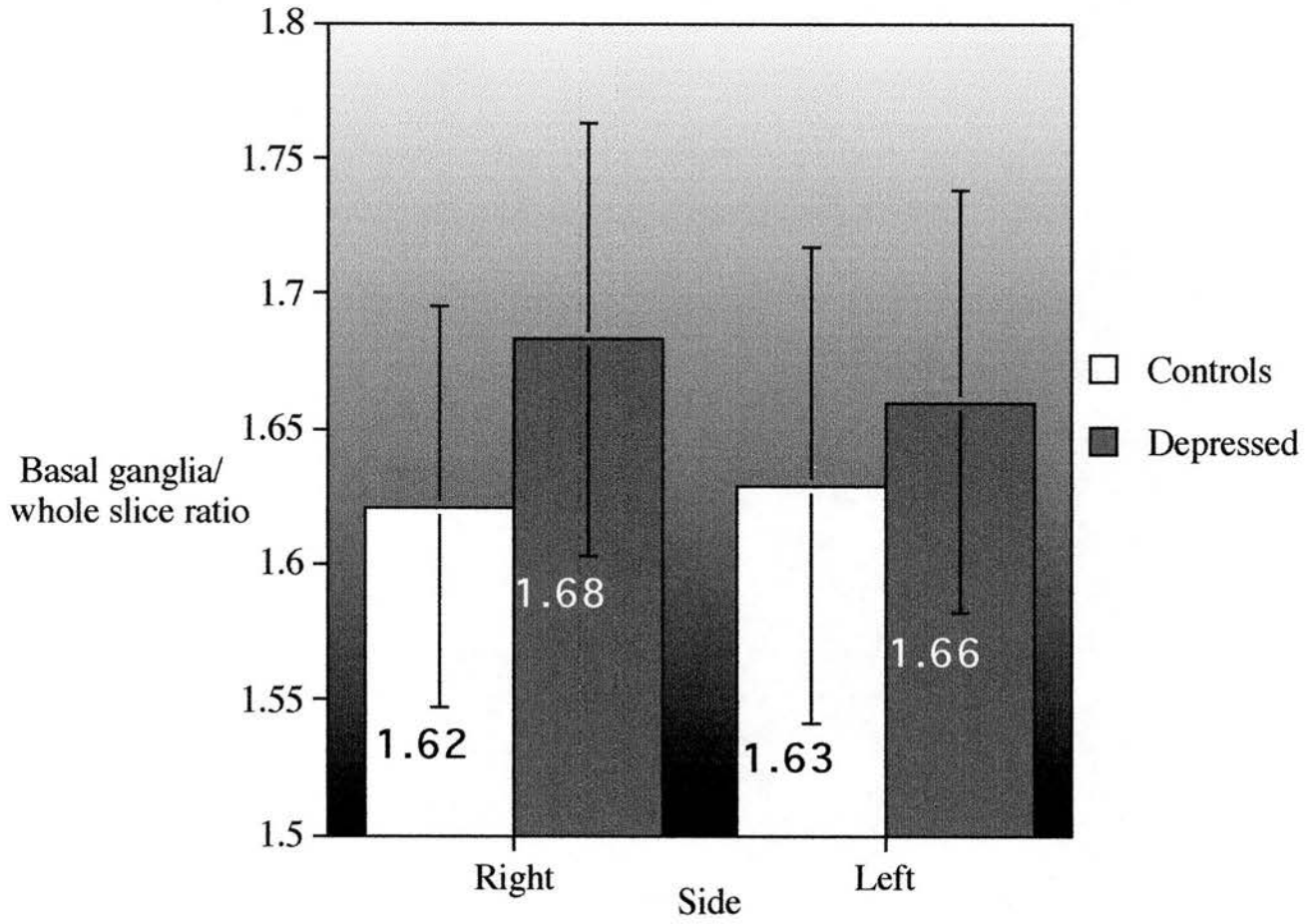


Figure 3.2 Scatter plot of striatal binding ratios with whole slice and frontal references in depressed patients and controls.

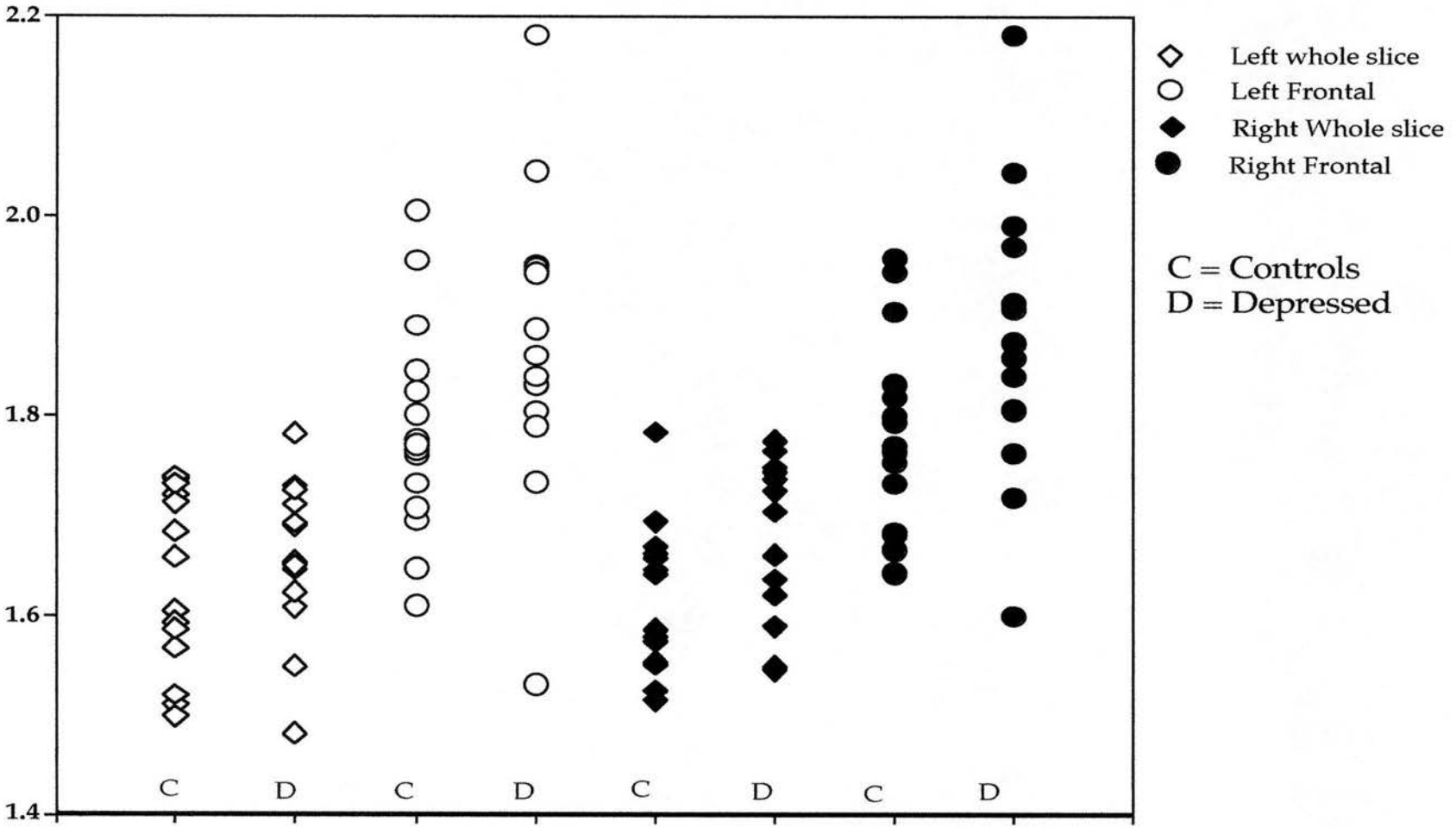


Table 3.2: Comparison of regional activity indices between groups, between gender, and between medication states

Regional Activity Index	**Controls (n=15)**	**Depressed (n=14)**	**Mann-Whitney U-test (p value)**	**Effect Size "d"**
Right striatum/ whole slice (SD)	1.621 (0.074)	1.683 (0.08)	**1.8 (0.03)**	**0.8**
Left striatum/ whole slice (SD)	1.629 (0.088)	1.66 (0.078)	0.7 (0.23)	0.37
	Medicated (n=10)	**Unmedicated (n=4)**		
Right striatum/ whole slice (SD)	1.71 (0.053)	1.61 (0.10)	-1.56 (0.12)	0.95
Left striatum/ whole slice (SD)	1.69 (0.049)	1.60 (0.10)	-1.56 (0.12)	0.85
	On antidepressants (n=7)	**Off antidepressants (n=7)**		
Right striatum/ whole slice (SD)	1.72 (0.049)	1.64 (0.09)	-1.45 (0.14)	0.99
Left striatum/ whole slice (SD)	1.69 (0.055)	1.63 (0.087)	-1.34 (0.18)	0.8
	Males (n=18)	**Females (n=11)**		
Right striatum/ whole slice (SD)	1.625 (0.086)	1.687 (0.062)	**4.9 (0.03)**	**0.9**
Left striatum/ whole slice (SD)	1.617 (0.084)	1.682 (0.067)	**4.87 (0.03)**	**0.87**

(1.66 (0.08) v. 1.63 (0.09), Cohen's d = 0.4, Mann-Whitney U-Test: Z=0.7, p=0.23). Ratios using the frontal region (figure 3.2) as reference produced essentially identical, albeit slightly more pronounced, group effects, (right: 1.88 (0.13) v. 1.7 (0.1), Cohen's

d= 1.0, Mann-Whitney U-Test: Z= 2.3, p=0.01; left: 1.88 (0.18) v. 1.80 (0.12), Cohen's d= 0.5, Mann-Whitney U-Test: Z= 1.6, p=0.05). The significant group difference for left striatal uptake ratios with a frontal reference region, together with the increase in effect size for both sides when using frontal reference regions, suggests a real effect in left striatum requiring larger samples to be statistically confirmed.

3.3.4. IBZM binding and medication

We examined the effect of concomitant medication that could potentially decrease dopaminergic activity in an indirect fashion, such as antidepressants and benzodiazepines, by comparing ten medicated patients against the four on no medication (table 3.2). No significant effect was found, although the observed effect sizes were large (d= 0.85- 0.95), with higher binding ratios in medicated patients. Further investigation is therefore merited as medication being a confounder. Not surprisingly, similar results were found comparing patients on (n= 7) and off (n= 7) antidepressants (d= 0.80- 0.99)

3.3.5. IBZM binding and gender

Across both groups, women had higher striatal (whole slice) uptake ratios compared with men (table 3.2) for both the left (1.68 (SD:0.07) vs. 1.61 (SD:0.08), d = 0.90) and the right side (1.69 (SD:0.06) vs. 1.62 (SD:0.09), d = 0.87). Although this effect of sex appeared greater in the control group (d= 0.9- 1.5) than in depressed (d= 0.1- 0.4),

there was no significant diagnosis by sex interaction ($F_{4,22}$= 0.49, p=0.75) Since both groups had equal ratios of males to females, sex was ignored as a confounding variable for the group comparison. Female patients were more retarded than male patients (1.8 (SD:0.98) vs. 0.75 (SD:0.71; Mann-Whitney U test, p = 0.04), but otherwise male and female patients were well matched for the items and the total score of the Hamilton scale, the Newcastle scale, and age.

3.3.6 Correlations between clinical and neuropsychological scales

There were positive correlations of total reaction time (r = 0.77, p = 0.001, 95% CI= 0.50 to 0.90), response initiation time (r = 0.74, p = 0.001, 95% CI= 0.44 to 0.89), and movement time (r = 0.48, p = 0.04, 95% CI= 0.05 to 0.76) with endogenicity of the depressive illness, as measured by the Newcastle scale. Reaction times did not correlate with depression severity, as estimated by the Hamilton scale total. Total reaction time (r = 0.47, p = 0.04, 95% CI= 0.03 to 0.76) and response initiation time (r = 0.51, p = 0.03, 95% CI= 0.09 to 0.78) however, positively correlated with the retardation item on the Hamilton scale. Maximal isometric contraction also correlated with the Newcastle scale (r = -0.56, p = 0.02, 95% CI= -0.80 to -0.16). Finally, performance on the verbal fluency task showed a trend towards negative correlation with retardation on the Hamilton scale (r = -0.39, p = 0.08, 95% CI= -0.71 to 0.06).

3.3.7 Correlation between IBZM uptake and neuropsychological test scores in depressed patients.

Table 3.3 shows the correlations of clinical and psychometric variables with striatal regional uptake ratios. Consistent with our hypothesis, we found positive correlations between movement time and regional uptake ratios, as well as negative correlations between verbal fluency and regional uptake ratios in the depressed group. Other measures of clinical retardation, such as the Hamilton-retardation score, response initiation time, and other timed neuropsychological tests were not significantly correlated with IBZM uptake in depressed patients. Notably, there were no correlations between uptake and severity of depression as measured by the Hamilton scale, type of depression as measured by the Newcastle scale, or age of the patient. An exploratory analysis of the Hamilton items showed that there was a strong negative correlation between the suicide item and IBZM uptake (right: $r = -0.70$, $p = 0.002$, 95% CI= -0.88 to -0.35; left: $r = -0.63$, $p = 0.008$, 95% CI= -0.85 to -0.24), suggesting that high suicidality was associated with more normal striatal IBZM uptake.

Table 3.3: Correlation of RAIs with clinical and neuropsychological scores

	Right striatal binding ratio		Left striatal binding ratio	
	rho	95% c.-i.	rho	95% c.-i.
Age	-0.22	-0.62 to 0.27	-0.24	-0.63 to 0.25
NART IQ	0.15	-0.33 to 0.57	0.13	-0.35 to 0.56
HRSD score	-0.2	-0.60 to 0.29	-0.18	-0.59 to 0.31
Newcastle scale score	0.03	-0.44 to 0.48	0	-0.46 to 0.46
APSAQ	0	-0.46 to 0.46	-0.07	-0.51 to 0.40
BFS total	-0.09	-0.53 to 0.39	-0.11	-0.54 to 0.37
BFS mood	-0.05	-0.50 to 0.42	-0.11	-0.54 to 0.37
BFS fatigue	-0.12	-0.55 to 0.36	-0.06	-0.51 to 0.41
Isometric contraction	0	-0.46 to 0.46	0.01	-0.45 to 0.47
Retardation item from HRSD	0.21	-0.28 to 0.61	0.19	-0.30 to 0.60
Total reaction time	0.27	-0.22 to 0.65	0.26	-0.23 to 0.64
Response intiation time	0.04	-0.43 to 0.49	0.03	-0.44 to 0.48
Response movement time	**0.59****	**0.18 to 0.83**	**0.60****	**0.19 to 0.83**
DSST	-0.04	-0.49 to 0.43	-0.04	-0.49 to 0.43
Trails-A	-0.08	-0.52 to 0.39	-0.04	-0.49 to 0.43
Trails-B	-0.05	-0.50 to 0.42	-0.07	-0.51 to 0.40
Verbal fluency	**-0.56****	**-0.81 to -0.13**	**-0.52***	**-0.80 to -0.09**
AVLT (total)	0.14	-0.34 to 0.56	0.18	-0.31 to 0.59
Delayed recall	0.24	-0.25 to 0.63	0.3	-0.19 to 0.67
Delayed recognition	0.01	-0.45 to 0.47	-0.01	-0.74 to 0.45

Table 3.4: Scores on the three personality questionnaires in the control group

EPQ	n=11	TPQ	n=10	NEO-5	n=10
Neuroticism	7.73 (5.85)	Harm Avoidance	7.1 (5.5)	Neuroticism	70.3 (18.1)
Psychoticism	2.64 (1.91)	Reward Dependence	15.8 (7.9)	Openness	120.7 (12.6)
Extraversion	15.45 (2.58)	Novelty Seeking	17.3 (9.1)	Extraversion	121.1 (9.2)
				Agreeableness	121.9 (15.9)
				Concientiousness	111.6 (20.8)

SD in parentheses

3.3.8 Correlation between IBZM uptake and personality dimensions in controls.

Initially, eleven of the controls completed the EPQ prior to the scan. After having examined the correlations between specific binding and EPQ personality dimension scores, control subjects were re-contacted in writing requesting the completion of the TPQ and NEO-5 inventories. Ten controls returned these completed questionnaires. Table 3.4 presents the mean scores for each of the inventories. Controls showed a range of Psychoticism scores on the EPQ from 0 to 8.

Table 3.5 summarises the correlation of personality dimensions with IBZM binding. There were negative correlations with psychoticism (right: $r = -0.48$, $p = 0.06$, 95% CI= -0.80 to 0.06; left: $r = -0.75$, $p = 0.004$, 95% CI= -0.91 to -0.37, figure 3.3) and positive correlations

Table 3.5: Correlations between scores on personality inventories and regional activity indices.

Inventory	Left Striatal binding ratio	Right Striatal binding ratio
EPQ		
Neuroticism	0.22	**0.56***
Extraversion	-0.14	0.29
Psychoticism	**-0.75****	-0.48
TPQ		
Harm Avoidance	0.41	0.48
Reward Dependence	**0.57***	**0.60***
Novelty Seeking	0.27	0.36
NEO-5		
Neuroticism	0.32	0.45
Extraversion	-0.14	-0.05
Openness	-0.22	-0.22
Agreeableness	-0.03	0.14
Conscientiousness	-0.12	-0.15

* $p < 0.05$ ** $p < 0.005$

between neuroticism and striatal IBZM uptake (right: $r = 0.56$, $p = 0.035$, 95% CI= 0.05 to 0.84; left: $r = 0.22$, $p = 0.26$, 95% CI= -0.34 to 0.67), but no correlations with extroversion in the EPQ (Eysenck & Eysenck 1975). This partially confirms results previously published by Gray and co-workers (Gray *et al*, 1994). The same correlations were found when repeated using frontal regions as reference. In the TPQ, reward dependence correlated positively with striatal binding (right: $r = 0.60$, $p < 0.05$; left: $r = 0.57$, $p < 0.05$) (figure 3.4 and 3.5), but not with novelty seeking or harm avoidance.

Figure 3.3 Graph of left striatal IBZM binding ratio and psychoticism score from the EPQ in 11 control subjects

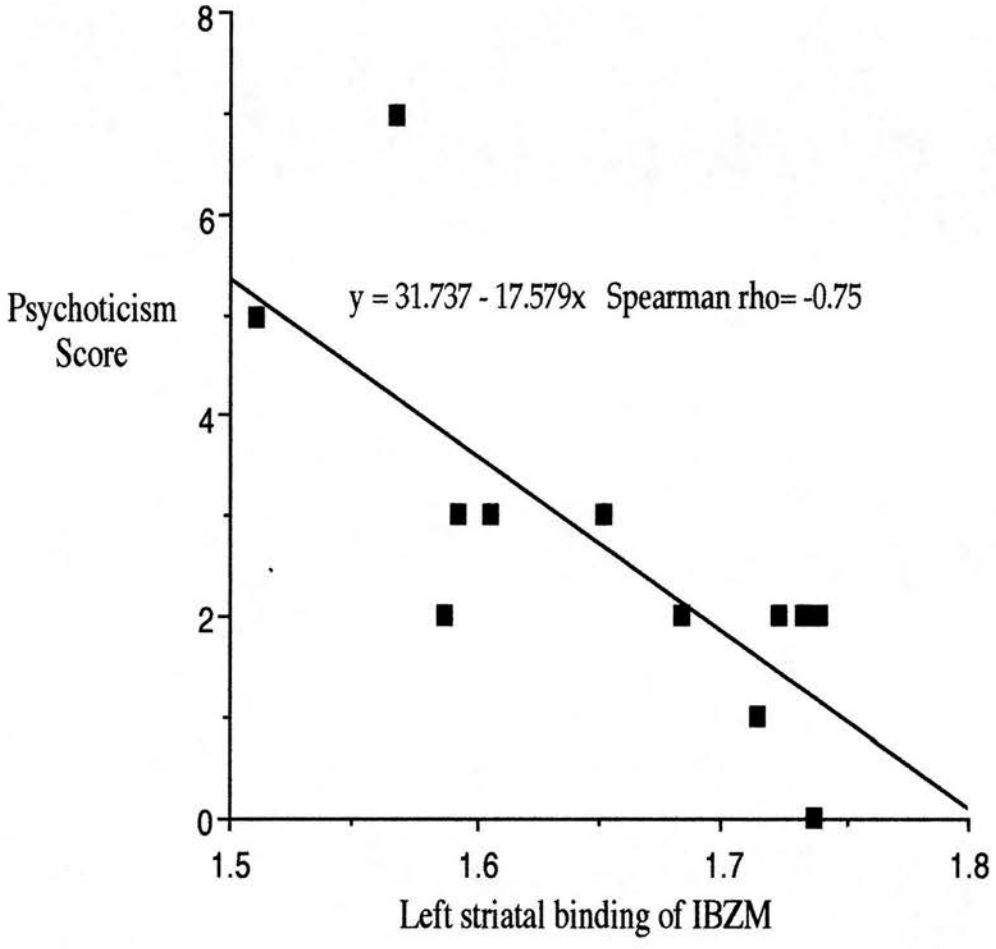


Figure 3.4 Graph of Reward Dependence and right striatal binding ratio in 10 control subjects

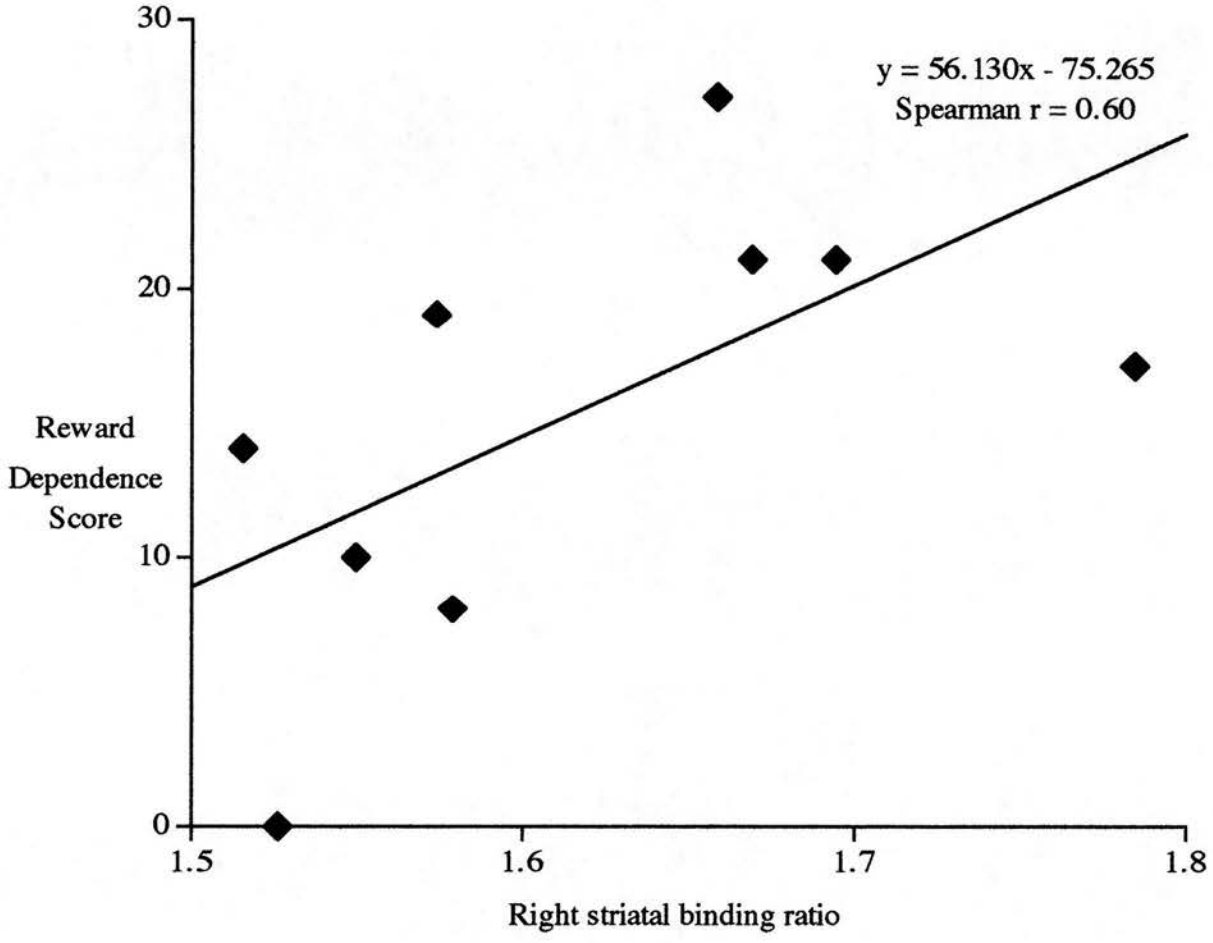
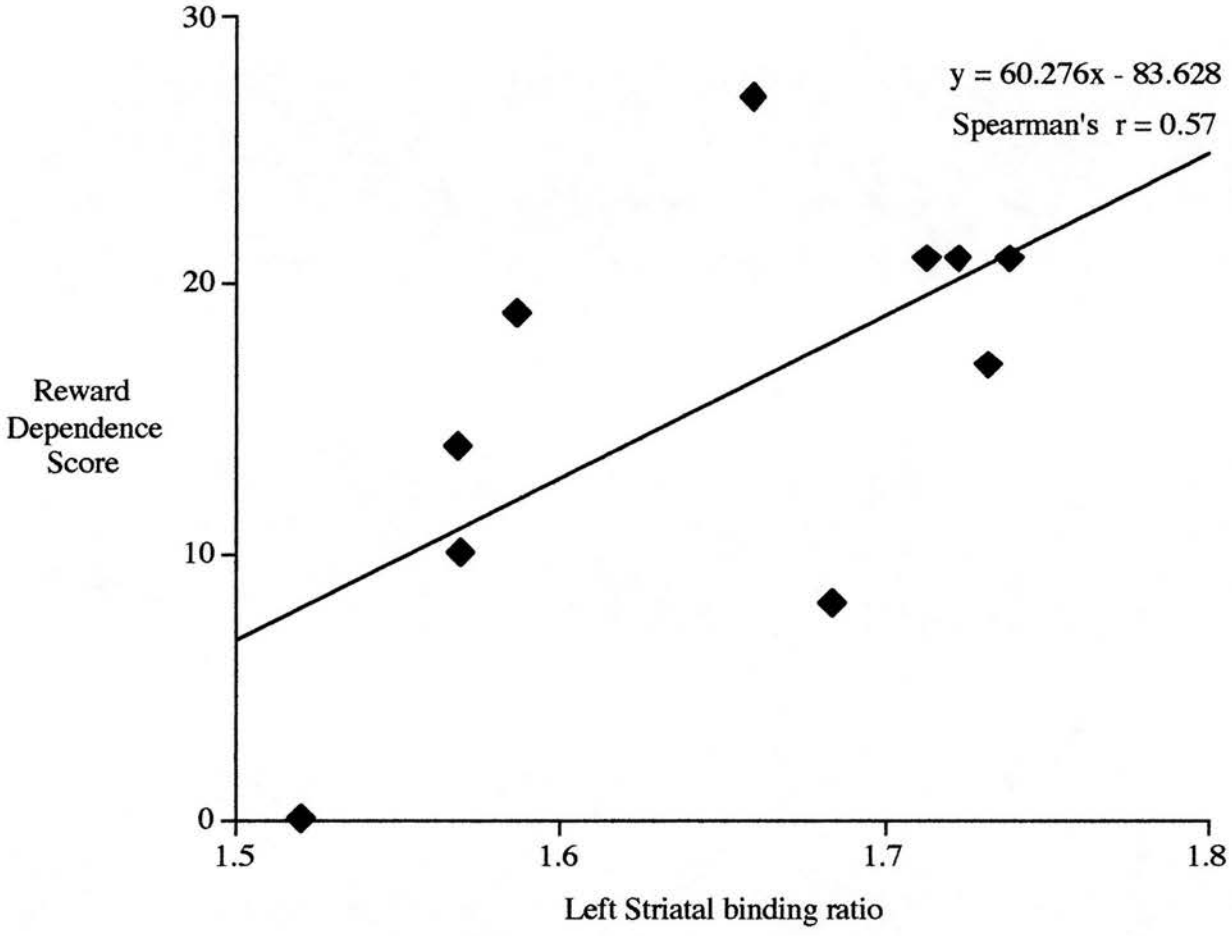


Figure 3.5- Graph of Reward Dependence and left striatal binding ratio in 10 control subjects



3.4 DISCUSSION

3.4.1 Group differences in IBZM binding

3.4.1.1. Influence of diagnosis

We were able to confirm that there is higher IBZM binding in the right striatum of depressed patients compared with healthy volunteers. There was a smaller difference in the left striatum, which did not reach statistical significance, even if a frontal reference region was used. Importantly, in depressed patients higher IBZM binding was correlated with measures sensitive to reduced speed of motor performance, such as movement time and verbal fluency, in which they had some degree of impairment compared to controls. Binding was not correlated with mood *per se*, grip strength or memory function.

That IBZM binding is higher in the right striatum of depressed patients has some support from Ebert's studies (Ebert *et al*, 1994a; Ebert *et al*, 1996), who showed that (retarded) patients had higher right-sided specific activity during a depressive episode, which normalised with drug treatment and with clinical response to sleep deprivation. The effect size of the group comparison was very similar to that reported in previous studies (Ebmeier & Ebert, 1996), suggesting a moderate, but robust effect. This finding has interesting parallels with SPET cerebral perfusion studies in depression. We have found a 7.5% lower perfusion of basal ganglia in depressed patients compared with controls (Austin *et al*, 1992b), which normalised on recovery (Goodwin *et al*, 1993).

3.4.1.2 Influence of gender and medication

IBZM binding differed between the sexes, with women having higher binding suggesting sexual dimorphism in the human striatal dopamine system. This effect was statistically independent of diagnosis and did not confound the comparison of sex- matched diagnostic groups. Because the sex effect appeared at least as pronounced within the controls, the main effect across diagnostic groups was not caused by the chance inclusion of more female retarded patients.

In previous studies of depression, the samples have either been all male (D'haenen & Bossuyt, 1994) or of unequal sex ratios (Ebert *et al*, 1994a; Ebert *et al*, 1996). Sex will, therefore, have to be controlled for as a confounder in future studies.

There is additional support for an effect of gender on dopamine function in humans. Pilowski et al (Pilowski *et al*, 1994) found greater left than right striatal IBZM binding in female, but not male controls. This difference was absent in schizophrenic patients, who showed greater left striatal uptake in both sexes. Plasma homovanillic acid levels 10 -70% higher in female than in male schizophrenics and controls have been reported (Koreen *et al*, 1994). This effect was more pronounced in patients acutely after receiving fluphenazine. Animal studies (Kazandjian *et al*, 1987); (Hafner *et al*, 1993) and limited human investigations have suggested modulation of dopamine function by oestrogen levels ((Wieck *et al*, 1991), (Best *et al*, 1992)). The explanation of the findings in terms of reduced pre-

synaptic release of dopamine or increased post-synaptic expression of receptors must remain tentative but merits further study.

None of the subjects received medication directly acting on dopaminergic receptors. However, there is some evidence that other neurotransmitter systems interact with dopaminergic function. Serotonergic agonism reduces extrastriatal dopamine concentrations, while acute serotonergic blockade increases concentrations (Dewey *et al*, 1995). Acute antidepressant treatment with a serotonergic reuptake inhibitor or a less specific drug, could, therefore be responsible for increased IBZM binding in patients. Similar effects on dopamine ligand binding have been demonstrated using drugs specifically acting on cholinergic and GABA-ergic transmission (Schloesserg *et al*, 1996). Although there were no significant difference in IBZM binding between medicated and unmedicated patients, and an initial investigation of the effects of antidepressant treatments showed a decrease rather than the predicted increase in IBZM binding (Ebert *et al*, 1996), we cannot exclude, at this stage, that the diagnosis effect may be confounded by the influences of sertonergic, benzodiazepine or anti-cholinergic indirectly on dopaminergic activity.

The difference between depressed patients and controls could be, equally, related to state or trait differences between the groups, or a combination of both. There is previous evidence that striatal IBZM uptake in depression may be state dependent (Ebert *et al*, 1994a; Ebert *et al*, 1996). A state effect on the occupancy of $D_{2/3}$ sites by

IBZM could be due to reduced striatal dopamine release or to an up-regulation of D_2 receptor density. A number of *in vivo* binding studies with benzamides have shown that decreased dopamine D_2 receptor occupancy can be the acute result of increased dopamine release or turnover (Hall *et al*, 1990; Logan *et al*, 1991; Laruelle *et al*, 1995) and the evidence from sleep deprivation suggests a similarly acute effect not likely to be produced by change in receptor number.

In contrast, there is indirect evidence suggesting a degree of irreversible change in the neurophysiological substrate, possibly dopaminergic, underlying psychomotor function in depression. Firstly, there is evidence that motor slowing persists even after treatment and recovery from depression (Beats, 1996) (O'Brien *et al*, 1993) (Abas *et al*, 1990). Second, the most consistent finding from structural studies in depressed patients is of reduced basal ganglia and frontal lobe volumes (Soares & Mann, 1997), also implying changes in the fronto-striatal dopaminergic system.

3.4.2 Correlations of striatal IBZM binding

3.4.2.1 IBZM uptake in depressed patients

Only four of the patients were clinically clearly retarded, but there were still measurable psychomotor differences between depressed and control patients, most prominently in movement time and isometric contraction. There were trends ($p<0.1$) also in other reaction time measures and verbal fluency. Maximal isometric contraction, response initiation and movement times were

correlated with endogenicity and clinically rated retardation correlated with reaction time, and weakly with fluency. These findings accord with the view that motor signs and, specifically, measures of performance may be more discriminating than subjective symptoms for identifying endogenous patterns of illness. It concords with a long standing tradition that places clinical retardation as a core symptom in depressive illness (Widlöcher, 1983; Parker *et al*, 1993; Rush & Weissenburger, 1993). The results do not, however, account for patients with the presence of agitation in endogenously depressed patients.

IBZM uptake correlated most strongly with relatively pure measures of motor function (speed of movement in the reaction time task) rather than clinical measures of mood, fatigue, grip strength or even retardation. This was despite the much greater group difference and within group variance for the patients compared with controls in the latter measures. This finding provides the first direct evidence suggesting that reduced receptor occupancy by endogenous dopamine in the basal ganglia has a primary effect on motor function in depression, although some limited evidence already exists to suggest acute reversibility of IBZM binding in depression (Ebert *et al*, 1996), IBZM uptake also correlated with verbal fluency and showed a trend with DSST performance. These are also tests that depend upon speed of motor performance and showed trends towards impairment in the depressed group. Performance of Trails A and B was neither impaired in the patient

group nor correlated with IBZM binding. Since the patients in this study did not on average display major psychomotor impairment, the correlations that did emerge were striking. Significant correlations could only be expected for the most sensitive of the measures or for those most directly related to striatal function In this regard the failure of mood to correlate with striatal IBZM binding is very interesting. Although this may have been due to small sample size, it could also suggest that IBZM might reflect motor slowing, regardless of cause. In support of this is evidence that striatal D2 receptors are associated with neuropsychological tasks involving psychomotor speed. Volkow et al (Volkow *et al*, 1998) using raclopride found an age dependent decline in striatal D2 receptor availability which most strongly correlated with a motor neuropsychological task (Finger Tapping Test) but also with most tasks involving frontal brain regions, involving tasks of abstraction and mental flexibility, and attention and response inhibition.

The strong negative correlation of IBZM uptake with suicidality could not be explained by sex differences and was otherwise unexpected. It could reflect the anecdotal clinical observation that activated depressed patients are at increased risk of suicide; this occurs classically after alleviation of psychomotor retardation by treatment, without an improvement of affect.

3.4.2.2 Correlations of IBZM uptake in healthy controls

The results suggest that the EPQ and TPQ may both have dimensions measuring behaviours related to striatal dopamine $D_{2/3}$ receptor

availability at rest. A lower IBZM binding ratio, corresponding to higher tonic striatal dopamine release and/ or lower striatal dopamine $D_{2/3}$ receptor density correlated with lower reward dependence on Cloninger's Tridimensional Personality Questionnaire and correlated with higher Psychoticism scores (i.e. more tough-minded) on Eysenck's Personality Questionnaire (left striatum particularly). Novelty seeking as well as all of the dimensions from the NEO-5 inventory did not correlate with IBZM binding.

There was also a positive correlation between neuroticism and the right striatal binding ratio. This is of particular interest, as neuroticism is a strong predictor of later depressive breakdown (Hirschfeld & Klerman, 1979; Angst & Clayton, 1986; Hirschfeld *et al*, 1986) and psychiatric morbidity (Duggan *et al*, 1995; Young *et al*, 1995; Krueger *et al*, 1996). As yet, no convincing biological correlate of neuroticism has been found to provide external validity, but it is interesting that other personality inventories often identify a dimension similar to neuroticism (e.g. neuroticism dimension in the NEO-5, (Costa & McCrae, 1992) and harm avoidance dimension in the TPQ, (Cloninger, 1987). It is also interesting that higher neuroticism is associated with higher right striatal IBZM binding. Increased right striatal binding was also found in the depressed patients. Neuroticism has been found to be high in patients when depressed and reduces on recovery. Thus, the potential contribution of trait differences to increased IBZM binding should not yet be discounted for depressive illness.

The lack of correlation with novelty seeking merits comment. Although Cloninger suggests that novelty seeking is a dopamine related dimension, evidence is equivocal. Studies of alcohol or drug misusers have suggested that novelty seeking may be related to dopamine activity (Cloninger, 1995). However, patients do not represent physiological normality, making it difficult to generalise to the healthy population. Genetic studies linking dopamine receptor subtypes and novelty seeking have also yielded diverging evidence (Benjamin *et al*, 1996; Ebstein *et al*, 1996; Malhotra *et al*, 1996). Finally, Psychoticism may be more closely correlated with reward dependence than novelty seeking (Zuckerman & Cloninger, 1996). It is therefore not surprising that novelty seeking did not correlate with IBZM binding.

3.4.3 Limitations and methodological considerations

The major limitation of the study is the small sample sizes. The main effect would be to reduce the power of the study, making it more likely to produce a false negative result. Power calculations suggest that to detect an effect size of 1.0 (or 0.5) in 80% of equal sized samples using a 2-tailed ǂ of 0.05, seventeen (64) subjects would need to be examined in each group (Cohen, 1988). It seems likely that there may be an effect of diagnosis on left striatal uptake which is missed due to lack of power. To counter this, there were a large number of tests. Thus, significant results could have been detected because of the large number of comparisons made. Similarly, the correlations between motor speed and uptake, and personality

dimensions and uptake, being dependent on a small data set are notable. Further studies with larger samples are thus required to confirm these results.

Unlike PET imaging, SPET receptor imaging can yield only semi-quantative measures of receptor availability and requires the choice of a reference region. Specific striatal binding ratios were calculated using whole slice activity as the reference region. As is demonstrated, using a frontal reference produces essentially the same results with a slightly greater effect size, but with greater variability. Whole slice references thus provides a more conservative estimate of striatal IBZM binding and makes it more likely that any effect may be missed. Frontal activity which is low, may also be subject to the effect of changes in frontal perfusion which is known to decrease in patients with depression. The use of reference regions within the same brain assumes that non-specific binding is the same for different subjects. However, this is not necessarily correct (Laruelle *et al*, 1995), thus leading to a greater difficulty in detecting between subject differences. Specific binding during the plateau phase after an i.v. bolus injection is further dependent on tracer washout from plasma, Plasma washout rates may vary in different groups of subjects, again affecting results (Laruelle *et al*, 1995).

The striatum was measured as a single region of interest, despite it being known that it is functionally heterogeneous. Moreover, the distribution of D2 and D3 receptors is know not to be homogeneous within the striatum. However, the spatial

resolution of SPET precludes the division of the striatum into even caudate and putamen unlike PET imaging. The effect would be to reduce the effect size if changes occurred only in a part of the striatum. Correlations with neuropsychological measures may also be expected to be wide-ranging, relating to the striatum's diverse range of functions. Thus, it is not surprising that striatal activity reflects motor slowing in depression. reflects gender differences and reflects personality traits.

3.5 Summary

There are four main findings:

1. Depressed patients have higher, particularly right, striatal IBZM binding than controls. Acute medication effects cannot be ultimately discounted in this study.
2. Increased striatal IBZM binding in the depressed patients was correlated with objectively measured motor slowing and not with mood, fatigue or hand grip.
3. Women had higher IBZM binding bilaterally, independent of diagnosis.
4. Psychoticism and neuroticism from the EPQ, and reward dependence from the TPQ correlated with IBZM binding, implying that the normal variation in limbic striatal receptors may be associated with normal variation in personality.

IBZM binding at striatal $D_{2/3}$ is dependent on two factors; receptor density and basal intrinsic dopamine release. Depression could be associated with reversible or irreversible differences in either of these. A cross-sectional study such as this using SPET imaging cannot definitively distinguish between these effects. However, from the currently available evidence, it would seem likely that increased binding is associated with a reduction in dopaminergic function either reflected in reduced dopamine release and/or dopamine receptor up-regulation. The observed associations between dopamine receptor binding and the motor slowing of the depressed state may, at least in part, reflect a more stable trait of depressed patients. Furthermore, the available evidence would

suggest that the effect personality probably represent normal variance in receptor density. The explanation of the sex difference in terms of reduced pre-synaptic release of dopamine or increased post-synaptic expression of receptors must remain tentative but merits further study. If these results were to be confirmed, future imaging studies would need to control for variation in D2/3 receptor density and/or baseline dopamine release, as both gender and personality were strong effects and could act as confounders especially in studies with small samples.

CHAPTER 4:

STRUCTURAL AND FUNCTIONAL BRAIN MARKERS OF TREATMENT RESISTANCE AND CHRONICITY IN MAJOR DEPRESSION

CHAPTER 4: STRUCTURAL AND FUNCTIONAL BRAIN MARKERS OF TREATMENT RESISTANCE AND CHRONICITY IN MAJOR DEPRESSION

Parts of the chapter have been published together with K.P. Ebmeier as a book chapter in (Shah & Ebmeier, 1998)

4.1 Introduction

One challenge to the present day nosology of depression is to find differences in aetiology, pathology and prognosis within an apparently clinically homogeneous syndrome. For this purpose, modern imaging techniques may be able to define brain differences associated with differences in outcomes.

Recent functional imaging studies suggest that the perfusion and metabolic changes associated with depression may not fully reverse in some groups of patients. Accordingly, high resolution structural studies also find differences in some groups of depressed patients. In the following chapter, it is first argued that treatment resistance defines a group of patients who may have structural brain differences compared to those with a good outcome. Then, the preliminary evidence of functional and structural abnormalities associated with a poorer prognosis is examined.

4.2 Using treatment outcome to define a homogeneous group

It is surprising that treatment outcome has not been used more often to define subgroups of patients with depression. This may partially stem from traditional psychiatric wisdom, which contends that mood disorders have a good outcome, in contrast to the poor prognosis of dementia praecox (Kraepelin, 1912). However, accumulating epidemiological evidence suggests that a significant proportion of patients has a chronic course and suggests that they form a distinct group:

a. Of depressed patients attending psychiatrists, up to 20% develop a chronic, treatment resistant illness (Keller *et al*, 1982; Kiloh *et al*, 1988; Lee & Murray, 1988; Scott, 1988), i.e. an illness that fulfils diagnostic criteria for at least two consecutive years. Although the NIMH Psychobiology study was carried out with predominantly inpatients (Keller *et al*, 1982; Keller *et al*, 1984) referred to a tertiary referral centre, other studies have found similar rates of chronicity in out patients and community based samples in non-elderly age groups (Weissman & Klerman, 1977). Further, these seminal studies were carried out prior to the modern treatment era. However, two more recent studies have indicated that the long term outcome from depression still remains poor in up to 20% ((Kiloh *et al*, 1988; Lee & Murray, 1988)). Although recovery does continue after two years of illness, the rate of recovery slows substantially after the first twelve to eighteen months (Keller *et al*, 1982; Keller *et al*, 1984), suggesting that patients with chronic illness

may, by their very nature, form a distinct subgroup, possibly with associated irreversible, i.e. structural brain changes.

b. Poor outcome from depression is associated with a number of factors, the best established being advanced age, and increased duration of the illness episode prior to treatment (Scott, 1988). Each of these suggest distinct aetiological mechanisms:

1. Advancing age: The bad prognosis in terms of both continuing morbidity and mortality of depression in the elderly was strikingly observed initially by Murphy and co-workers (Murphy, 1983; Murphy *et al*, 1988). Since then, evidence suggests that late onset depression (first episode after the age of 65) is associated with an excess of vascular risk factors (Fujikawa *et al*, 1994), with brain changes, particularly white matter hyperintensities (WMHs), and possibly with greater treatment resistance, mortality and morbidity (Hickie *et al*, 1995; Lesser *et al*, 1996; O'Brien *et al*, 1996; Krishnan *et al*, 1997; Videbech, 1997; Yanai *et al*, 1998) but with the absence of a family history of affective disorder, with fewer other predisposing aetiological factors found in younger age groups (Post, 1968; Alexopoulos *et al*, 1992; Fujikawa *et al*, 1996). In fact, it has been suggested that late onset depression may include a large proportion of patients with depression secondary to cerebrovascular disease (Krishnan *et al*, 1997). A central finding associated with treatment

resistance is that of cerebral WMHs. A review of the aetiology and clinical correlates of WMHs is therefore presented later.

2. Illness duration: At worst, longer illness periods without remission may result in a progressive, maybe permanent damage to the neural systems needed for recovery. One potential mediator of such damage is cortisol. Patients with depression show dysregulation of the hypothalamic-pituitary-adrenal axis. Up to 70% of patients have raised cortisol, which is generally not suppressed by dexamethasone (Dinan, 1994). A persistent positive dexamethasone suppression test, despite apparent clinical improvement, may predict rapid relapse and possibly chronicity (Amsterdam *et al*, 1983; Targum, 1983). Animal work further suggests that chronically raised cortisol can cause hippocampal neuronal death, which in turn may result in dysregulation of the HPA-axis (Sapolsky *et al*, 1986; Jacobson & Sapolsky, 1991). Despite this circumstantial evidence, there has been very little direct clinical testing of this hypothesis. The functional and structural imaging studies providing indirect evidence for neuroanatomical change in treatment resistant patients is reviewed in section 4.4.

4.3 White matter hyperintensities and late onset depression

4.3.1 Pathological correlates of WMHs

A great deal of interest has been taken in periventricular and subcortical white matter hyperintensities (WMHs) on MRIs. Originally called "unknown

bright objects", the aetiology of these discrete areas of signal hyperintensity on T_1- or T_2-weighted images is not clearly understood. There has been a tendency to attribute all such lesions to vascular causes, but it is probably better to follow Hachinski (Hachinski *et al*, 1986) in describing WMHs as "leuko-araiosis", i.e. rarefied white matter without implying cause.

WMHs can be subdivided on the basis of their distribution and their spatial extent. Fazekas et al. (Fazekas *et al*, 1993) compared the *in vivo* and *in vitro* MRI appearances of WMHs with pathological findings and showed that ventricular cap and smooth ventricular halo WMHs were closely associated with subependymal gliosis and were probably due to altered CSF dynamics. In contrast, irregular periventricular hyperintensities (PVHs) and more severe, confluent deep white matter hyperintensities (DWMHs) corresponded to areas of arteriolar thickening, lacunar infarction and reactive gliosis, with early confluent DWMHs associated with perivascular myelin rarefaction, gliosis and fibre loss. Similar results were found in two other studies (van Swieten *et al*, 1991), (Chimowitz *et al*, 1992) making it likely that severe PVHs and DWMHs are related to atherosclerosis. Whether milder PVHs are independent of atherosclerosis, but related to physiological changes occurring with advancing age, is yet to be determined.

4.3.2 Risk factors for WMHs

Epidemiological studies suggest that WMHs are found with increasing age, with vascular risk factors and risk factors for stroke. The Rotterdam study for example, a prospective study of 111 subjects aged 55 years or more, found that WMHs were more pronounced in people with carotid atherosclerosis (Bots *et al*, 1993). People with WMHs also showed greater evidence of peripheral vascular disease, possibly of coronary artery disease and were older than people without lesions. In the Helsinki Ageing Brain Study (Ylikoski *et al*, 1995), most subjects (n=128, general population neurologically non-diseased cohorts taken at five year intervals from 55 years old) showed only mild hyperintensities on T_2 weighted MRI sequences, most frequently in the periventricular areas. They concluded that white matter hyperintensities in normal cohorts were related especially to age, to "silent infarcts" and atrophy and to some vascular risk factors. Hence, there is strong evidence that these lesions are associated with advancing age and vascular risk factors.

4.3.3. Functional effects of WMHs in non-patient populations

The functional effects of WMHs in healthy elderly subjects are still uncertain, possibly since WMHs have been measured in a variety of ways. The evidence suggests that there may be an association between WMHs and measures of executive function, mental speed and attention. Ylikoski et al. (Ylikoski *et al*, 1995) in a large community sample found

that periventricular hyperintensities in particular were associated with reductions in measures of mental speed and ability on complex tasks. They suggested that such lesions might be an index of increasing brain vulnerability. Schmidt et al. (Schmidt *et al*, 1993) examining a large population sample (n= 150) found that subjects with WMLs, after controlling for age, had deficits in complex tasks, suggesting reduced mental speed. Further evidence from the Rotterdam study (n= 111) also found healthy subjects with WMHs to be impaired in cognitive tasks associated with executive function, mental speed and memory (Breteler *et al*, 1994a; Breteler *et al*, 1994b), though this was not significant after adjusting for age and education. This was similar to Tupler et al. (Tupler *et al*, 1992) in a study of 66 healthy volunteers. An interesting explanation has been offered by Boone et al. (Boone *et al*, 1992), who measured the total volume of tissue affected by WMHs in 100 normal subjects, and suggested that a threshold volume needed to be affected for there to be a measurable effect on cognitive tasks. This may be reasonable, since in most qualitative studies, cognitive impairment is particularly associated with the severe end of the spectrum of WMLs. However, it remains speculative since there have not been any confirmatory studies. To summarise, population based studies of the healthy elderly population with a total sample size of nearly 500 subjects, suggest that WMHs may be associated with a small but significant effect on executive function and mental speed although it is not known if these lesions are causally related, are

markers of a generalised cerebral process, or an incidental epiphenomenon to possible cognitive changes.

4.3.4 WMHs and affective disorder

A large number of studies have examined the relationship between WMHs and affective disorder, particularly in older age (O'Brien *et al*, 1996). Drawing firm conclusions from these studies is hampered by the different methods of rating WMHs, by the selection of mixed (i.e. bipolar vs. unipolar) depressions, and varied duration of illness. Nevertheless, in comparison with elderly controls, elderly depressed patients have more numerous or more extensive WMHs. In elderly (>60 years) patients with depression severe enough to merit ECT, Coffey et al. (Coffey *et al*, 1990) found that patients with depression had more extensive DWMHs and PVHs compared to matched controls and that these were related to vascular risk factors. Subsequent studies suggest that DWHs (Coffey *et al*, 1990; Brown *et al*, 1992; Greenwald *et al*, 1996) and PVHs (O'Brien & Ames, 1996) may be more severe, but not more numerous in elderly depressed patients.

Few studies have directly examined the possible association between vascular risk factors in patients with depression and WMHs. Studies either omit to measure risk factors, measure them in a non-standardised way or correlate them with merely the presence or absence of WMHs. Coffey et al. (Coffey *et al*, 1990), for example, found that WMHs in the

depressed group were associated with vascular risk factors. Miller et al. (Miller *et al*, 1994) selected subjects and patients without vascular risk factors, and found no significant difference in the presence, but found a trend for more severe DWMHs in depressed patients. That this difference was not significant was probably due to the relatively small sample size. This perhaps indicates that other factors apart from vascular pathology may contribute to DWMHs. O'Brien et al. (O'Brien *et al*, 1996) also found that even controlling for vascular risk factors and current blood pressure, depressed patients had more DWMHs than controls. Therefore, although it is tempting to speculate that late onset depression in particular is an illness with vascular aetiology (Krishnan *et al*, 1997), there is presently not the balance of direct evidence that can attribute the increased severity of DWMHs in old age depression wholly to excess vascular risk factors.

The association between WMHs and age of onset of depression implies that late onset depression differs in its aetiology from early onset depression. A problem lies in the definition of "late onset", which ranges from 45 to 65 years. The likelihood of finding group differences will vary with the assumptions made about underlying risk factor(s). If such a risk factor was proportional to age, dichotomising at different ages could yield significantly different results. However, if the relationship was non-linear, then different age cut-offs might generate similar results. Krishnan et al. (Krishnan *et al*, 1988) defined late onset as being >45

years and found increased DWMHs in late onset depression, although the two depressed groups were not matched for age. Miller et al. (Miller *et al*, 1994) and O'Brien et al. (O'Brien *et al*, 1996), defining late onset as >65 years, Figiel et al. (Figiel *et al*, 1991) as >60 years and Hickie et al. (Hickie *et al*, 1995) as >50 years also showed differences between late and early onset depression in terms of the presence of subcortical hyperintensities (Figiel *et al*, 1991) or in the extent of PVHs and DWMHs (Miller *et al*, 1994; Hickie *et al*, 1995; O'Brien *et al*, 1996). Also, two studies ((Lesser *et al*, 1996) (Salloway *et al*, 1996)) have compared the volume of WMH tissue between early onset and late onset depression. Both found that late onset depression was associated with greater WMHs than early onset, even though the definition of late onset differed between the two studies. It, therefore, seems likely that late onset depression is associated with more extensive areas of WMHs, particularly, DWMHs, above and beyond the effects of age.

4.3.5 WMHs in depression and cognitive impairment

From the studies of healthy controls, it may be expected that WMHs in late onset depression would be associated with greater cognitive impairment. Two volumetric studies (Lesser *et al*, 1996) (Salloway *et al*, 1996) found that late onset patients who differed from early onset patients in terms of DWMHs, also showed reduced performance on executive tasks and tasks of mental speed. Ebmeier et al (Ebmeier *et*

al, 1997) found that the severity of DWMHs correlated negatively with the MMSE, a global measure of cognitive function. Further preliminary evidence suggests that increasing WMHs characterise patients with a poorer treatment response (Hickie *et al*, 1995), who are functionally more impaired (Hickie *et al*, 1995). Thus, WMHs may be involved in producing cognitive impairment, a risk factor for (continuing) depression (Post, 1968).

4.3.6 Summary of WMHs in (late onset) depression

There is strong evidence that the presence of WMHs increase with age in healthy controls, and that late onset depression is associated with increased severity of these lesions. There is preliminary evidence that an increase in the extent of these lesions is associated with treatment resistance, poorer outcome and greater functional disability. There is reasonable evidence that the presence of DWMHs is associated with a small degrees of cognitive impairment in the asymptomatic elderly, and that depressed patients with large volumes of DWMHs have greater cognitive impairment. It is probable, though not yet conclusively proven that vascular disease is a major cause of the DWMHs and of late onset depression. Although there is some evidence that WMHs are also found in younger age depression, it is limited primarily to bipolar affective disorder; there is less convincing evidence for unipolar affective disorder (Soares & Mann, 1997).

It is not known if the site of DWMHs are importance. It has been proposed, for example, that particularly lesions of the basal ganglia or their connections may be associated with depression (Swerdlow & Koob, 1987). On the other hand, the load of tissue affected by DWMHs may be important for cognitive impairment (Boone *et al*, 1992; Lesser *et al*, 1996), which may act as a vulnerability factor for, and perpetuator of continued depression (Post, 1968; Ebmeier *et al*, 1997). Thus, WMHs may represent generalised age-related changes, vascular disease, or other as yet unidentified pathological processes, that produce cognitive impairment.

4.4 Evidence from perfusion and volumetric studies

4.4.1 Functional imaging studies and treatment resistance

There have been only a few functional studies directly examining treatment resistant patients, usually in comparison to controls (Morinobu *et al*, 1991). Mayberg et al (Mayberg *et al*, 1994) found blood flow reductions in bilateral frontal cortex, anterior temporal cortex, anterior cingulate gyrus and caudate compared to controls. The greatest decreases were seen in the inferior frontal and cingulate cortex. Bonne et al (Bonne *et al*, 1996) describes patients with medication resistant depression as having reduced perfusion in left superior temporal, right parietal and bilateral occipital regions. The ideal comparison in such studies is CTRD patients with patients who will eventually respond, to identify metabolic or perfusion patterns that may be found only in

non-responders. Thus, it is particularly interesting that Hornig et al (Hornig *et al*, 1997) found an increase in hippocampus-amygdala activity in CTRD patients compared with patients with treatment responsive depression.

If depression is fully reversible, regional perfusion or metabolism changes during depression should return to normal on recovery. This may not be the case. Recovery may involve more focused increases of activity in the basal ganglia and in fronto-cingulate cortex (Goodwin *et al*, 1993; Bench *et al*, 1995) (table 2.1), but not in temporal cortex. Since functional imaging may detect reduced activity of intact neurones, normal activity in disrupted cortical neuroterminals, or a combination of both, persistent reductions in perfusion may reflect grey matter change. With the limited evidence available, therefore, it appears that changes in temporal limbic structures may be associated with treatment resistance and chronicity.

Further evidence for a role of temporal lobe structures comes from studies of the elderly. In one study, periventricular high intensity signals, discussed above, were correlated with reduced perfusion in a large contiguous volume extending across both temporal lobes and around the ventricles (Ebmeier *et al*, 1997) implicating temporal lobe abnormalities in the development of depressive illness in late life. As patients with such hyperintensities may be more treatment resistant and may have a worse outcome (Hickie *et al*, 1995), it suggests temporal lobe changes are associated with chronicity/ treatment

resistance. As age of onset of depression was negatively correlated with perfusion in bilateral temporal cortices, and with fewer MRI abnormalities in patients with early onset depression, length of illness and chronic hypercortisolism were unlikely to be responsible for these perfusion changes. Changes at a molecular level, in functional and structural imaging also suggest a link between temporal lobe changes and increased vulnerability to continued depression (Sheline *et al*, 1996; Hornig *et al*, 1997; McEwen, 1997).

4.4.2 Volumetric studies and treatment resistance

The considerations discussed previously, regarding sample selection and methods of image analysis in functional imaging studies apply to structural imaging studies. It is, therefore, not surprising that such studies have also often had a diverse range of findings. There have not been any studies that directly address if treatment resistance is associated with structural brain differences. The evidence, therefore, is indirect.

In terms of generalised tissue loss, a recent meta-analysis of both CT and MRI studies (Elkis *et al*, 1995) concluded that patients with affective disorders had small increases in the ventricle-to-brain ratio (VBR) and indices of sulcal prominence (SP, a measure of focal cortical tissue loss), and that patients with affective disorders did not differ from those with schizophrenia (Elkis *et al*, 1996). Increased VBR and SP may be present particularly in the elderly group, and may be associated with

treatment resistance. It is perhaps not surprising that previous conventional reviews have concluded that there is no increase in the VBR in affective disorders, since the overall effect size is small, and the power of studies is often not sufficient to yield significant results.

The most pervasive criticisms of the VBR are that it reflects both global and focal tissue loss, and that increases are not diagnosis specific. Additionally, most studies only analysed a single slice of the acquired image. Together with the relatively subjective selection of the "right" slice in the "correct" orientation, the measurement of a one-dimensional variable obviously has many more spatial degrees of freedom than, say the determinations of a volume and is thus, liable to have greater measurement variability.

In terms of focal brain changes, a brief review is given here of findings in unipolar depression. There are four previous MRI studies that have rated or quantified frontal lobe volume. Reduced frontal brain width has been found in middle aged unipolar depressives (Krishnan *et al*, 1992) and in elderly unipolar depressives prior to ECT (Coffey *et al*, 1993). This finding has not been replicated in younger bipolar mood disorder patients (Coffman *et al*, 1990) (Schlaepfer *et al*, 1994). With regards to the temporal lobe, most studies have been confined to patients with bipolar affective disorder, where there is mixed evidence of all, "no-change", increases or decreases in volume. Only one studies (Coffey *et al*, 1993) had a large number of patients with unipolar depression and showed no difference in temporal lobe volume. This

latter study is of interest since it seems to suggest that elderly severely depressed and possibly treatment resistant patients may not show temporal lobe structural change.

The amygdala-hippocampal complex has been of intense interest because of its role in memory (known to be impaired in depression), and because it may be a structure vulnerable to the effects of corticosteroids, and thus a candidate structure to be affected by chronicity. However, most volumetric studies of unipolar patients have, so far, been negative. Both Coffey et al. (Coffey *et al*, 1993), who examined mainly elderly patients awaiting ECT, and Axelson et al. (Axelson *et al*, 1993), examining younger inpatients, found no reduction in hippocampal volume. Interestingly, Krishnan et al. (Krishnan *et al*, 1991) found a reduction in T_1 relaxation time in this area in a sample of elderly unipolar depressed patients. More recently, Sheline et al. (Sheline *et al*, 1996) reported a reduction in hippocampal volume in a small sample of elderly women with recurrent unipolar depression, who were asymptomatic at the time of imaging. There are a number of possible explanations for this discrepancy. First, apart from the latter study, the resolution of the MRI images may have been insufficient to detect change in the hippocampus (typical slice thickness of 5mm vs. up to 1.25 mm presently). Second, as most studies use ROI analysis, localised changes may not have been detected if the volume of the whole amygdala/hippocampal complex was measured. Finally, samples may have been heterogeneous: older patient samples may have included

both late and early onset patients and younger samples both chronic and non-chronic patients.

There is better evidence that patients with unipolar depression, particularly with increasing age, have smaller basal ganglia. Husain et al. (Husain *et al*, 1991) examining 41 unipolar patients (mean age: 55.3) and Krishnan et al. (Krishnan *et al*, 1992) examining 50 patients (mean age: 48.3) found bilateral reduction in putamen and caudate volume, whilst Dupont et al. (Dupont *et al*, 1995) examining 30 unipolar (mean age: 36.6) and 36 bipolar patients found a similar trend in only unipolar depression. Reductions were also found in 25 elderly (mean age: 74.1) patients with unipolar depression (Krishnan, 1993). Finally, two controlled MRI studies have found reductions in cerebellar volume (Escalona *et al*, 1993) and cerebellar vermis (Shah *et al*, 1992) in relatively middle-aged patients.

4.4.3 Conclusions

In summary, conventional volumetric analysis shows that patients with unipolar depression may have reductions in frontal lobe and basal ganglia (particularly in the elderly), and cerebellum. The evidence for thalamic reductions is scant, and for the temporal lobe, equivocal. There is uncertainty about changes in the amygdala/hippocampal complex partially through reservations about image resolution and the patient groups used. Nevertheless, there is some evidence that hippocampal atrophy may be present, despite recovery from depression,

supporting the notion that repeated exposure to depression has an enduring structural effect.

Structural differences, at least in elderly depressed patients may be associated with treatment resistance (Hickie *et al*, 1995). However, it is not known if this extends to younger patients since the balance of causes of depression may be age dependant: depression first presenting in old age may involve less genetic predisposition, but may be related to vascular disease or to age related degenerative processes (Alexopoulos *et al*, 1992; Axelson *et al*, 1993; Hickie *et al*, 1995; Soares & Mann, 1997).

There are inconsistencies, between the evidence from structural studies suggesting fronto-striatal volume reductions, and perfusion and metabolic studies suggesting recovery in these areas on remission, but enduring perfusion deficits in temporal regions. There is, therefore a need to examine chronic, treatment resistant depression in middle-aged patients, who would have been less subject to the age-related degenerative and vascular pathologies found to be important in late onset depression in the elderly. This is the subject of the next studies.

CHAPTER 5:

CHRONIC, TREATMENT RESISTANT DEPRESSION - MRI CHANGES AND CLINICAL CORRELATES.

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5.0 ABSTRACT

Severe, chronic, treatment resistant depression (CTRD) is a condition that is well recognised, but little understood. Though apparent intractability may reflect brain abnormality, this has not previously been specifically examined. The MRI images of the brains of twenty patients with major depression lasting for two years or more were compared with twenty controls and twenty other patients showing complete recovery from depression. Subjects were individually matched for age, sex, years of education and premorbid IQ. A fully automated, operator independent voxel based method was used to segment grey, and white matter and CSF allowing group comparisons and correlations to be made. Patients with CTRD had altered grey and white matter densities in the left hippocampus and rostral anterior cingulate. There was evidence of right putamen and right frontal lobe atrophy, confirmed on conventional volumetric analysis, with smaller left frontal reductions, concentrated more in white matter. Only grey matter density was reduced in left temporal neocortex. Neocortical reductions were related to the severity of illness over time, and not duration of illness. Older age and increasingly severe motor retardation was associated with

medial prefrontal grey matter reductions (Broadman areas 9 and 10) in the CTRD group. In the RD group, medial prefrontal grey matter reductions also correlated with age and age of onset. Hippocampal and anterior cingulate changes were independant of illness duration and severity, and from ECT treatment. The study is the first to report localised tissue abnormalities in patients with CTRD using voxel based analysis and broadly supports the notion of a "fronto-subcortical" or "fronto-striatal" dementia. Voxel based analysis provided a more sensitive and complete analysis than conventional volumetry, allowing the detection of a grade of MRI abnormalities. The results challenge the accepted view of depression as a functional and fully reversible illness, implying that more permanent brain changes may be associated with chronicity. Prospective studies are required to determine whether these differences predate the onset of depression or are the result of the chronic illness process or its treatment.

5.1 INTRODUCTION

5.1.1. Background

Depression is one of the most common clinical problems presenting to psychiatrists, and has an estimated lifetime incidence of 25% in the general population (Rorsman *et al*, 1990). Of those, about 10% present to psychiatrists, possibly on the basis of depression severity or initial treatment non-response. Up to one in five of these patients with unipolar depression follow a chronic, treatment resistant course (Keller *et al*, 1982), (Scott, 1988), i.e. an illness fulfilling diagnostic criteria for at least two consecutive years. Chronic treatment resistant depression (CTRD) is, therefore, important for psychiatric practice, but little is known of its specific aetiological characteristics. The established clinical associations are with duration of symptoms before treatment and with age (Scott, 1988). The very nature of refractory illness suggests that some permanent change in brain structure may have occurred, but past neuroimaging studies have either ignored the issue or provided only limited evidence for biological correlates of treatment resistance or chronicity (Morinobu *et al*, 1991; Mayberg *et al*, 1994). Studies which have found structural differences in depressed patients associated with treatment resistance have been in the elderly (Hickie *et al*, 1995).

However, since the balance of causes of depression may differ at different ages, these results may not apply to younger age groups.

5.1.2 Previous neuroimaging studies

Until recently, neuro-imaging studies have identified the anatomical substrates of depression in rather broad terms and have often provided conflicting results. During depression, regional perfusion is diffusely reduced in frontal and temporo-limbic cortex, as well as in the basal ganglia, but may be increased in some cingulate regions and ventromedial prefrontal cortex in particular groups of depressed patients (Mayberg *et al*, 1997; Drevets, 1998; Ebert, 1998). Recovery may involve more focused reversals of activity in the basal ganglia and in fronto-cingulate cortex (Goodwin *et al*, 1993; Bench *et al*, 1995). Since functional imaging may detect reduced activity of intact neurones, normal activity in disrupted cortical neuroterminals, or a combination of both, reductions in perfusion may sometimes reflect structural changes in grey matter. In fact, Mayberg et al (Mayberg *et al*, 1997) has recently suggested that responders and non-responders to treatment can be distinguished by the presence of hyper - and hypo - perfusion in the rostral cingulate (Brodmanns' area 24).

Similarly, Drevets et al (Drevets, 1998) proposes subgenual anterior cingulate (Brodmann area 25) hypoperfusion may be a trait marker for familial depression, partially explained by grey matter reduction in this area. Both these findings may be associated with structural changes.

Structural studies using CT or MRI have shown non-specific changes, such as ventricular enlargement that may reflect cortical atrophy or basal ganglia changes or a combination of both (Soares & Mann, 1997). So far, localised frontal lobe atrophy, especially in the elderly with severe depression (Coffey *et al*, 1993), and reduced caudate nucleus volume in unipolar patients (Soares & Mann, 1997; Krishnan *et al*, 1992), have been the most reliably reproduced results. There is also one report of hippocampal atrophy found in a small cohort of elderly depressed patients with recurrent depression (Sheline *et al*, 1996), which may be important if reproduced.

5.1.3 Methods of image analysis

The absence of spatial precision in neuroimaging studies, as well as apparently contradictory findings are partially due to the limitations of the region of interest (ROI) approach to image analysis. For structural scans this involves laborious slice by slice measurement of the volumes of local structures, and

has a number of limitations. Anatomical boundaries are usually arbitrary and assume functional homogeneity for the structure. Further, it assumes that any change occurs throughout the whole volume of interest or a majority part. Volumes are identified on a priori hypotheses, and therefore only a part of the data set (or image) is analysed. Measurements can be highly operator dependant, with reliability becoming lower for small volumed structures such as the hippocampus. Finally, only the volumetric aspect of the data and not the signal intensity is analysed.

As an alternative, the use of voxel based analysis (VBA) has recently been extended to analysing structural MRI (Wright *et al*, 1995), addressing some of the shortcomings of volumetric analysis. It has already transformed the approach to isotope based functional imaging (Friston, 1994; Friston *et al*, 1995b), where region of interest analysis was previously regarded as the "gold standard". With VBA, MRI scans of patients are first spatially transformed into a standard brain atlas space to remove variation in overall brain position, size and shape. Images are then segmented into three tissue compartments, grey matter, white matter and CSF, each of which may be compared between groups on a voxel by voxel basis. The technique for spatially transforming and segmenting images into different tissue types is fully

automated and operator independent (Wright *et al*, 1995). Additionally, the whole (image) data set can be statistically interrogated independent of hypotheses after appropriately correcting for multiple comparisons. Where hypotheses exist, these constraints can be relaxed. Tissue segments can also be subject to correlational analysis, matching structure with function or important clinical factors.

5.1.4 Aims of this study

In this study, voxel based analysis was used to compare the three tissue compartments (grey matter, white matter and CSF) between three subject groups- patients with chronic, treatment resistant chronic depression (CTRD), recovered (RD) patients, and normal healthy volunteers (C). If previous studies can be generalised to younger patients, it would be expected that the CTRD group would show grey matter density reductions in bilateral frontal and temporal regions, including the hippocampus and basal ganglia. It would also be expected that there would be corresponding white matter reductions and increases in CSF in appropriate regions. Following Mayberg's (Mayberg, 1997) and Drevet's (Drevets, 1998) studies, grey matter changes may also be expected in anterior cingulate regions. Further, grey matter density changes should correlate with clinical

dimensions - specifically, depression severity should correlate with medial frontal grey reductions and clinically rated retardation with basal ganglia and prefrontal grey matter on the basis of functional imaging studies(Austin *et al*, 1992b; Curran *et al*, 1993; Mayberg *et al*, 1994). These correlations in the chronic group would in effect confirm the biological significance of any observed group differences, as these differences would then be not only categorical, but also related to the underlying dimensions of function.

5.2 MATERIALS AND METHODS

5.2.1 Subjects

All subjects gave informed written consent following a protocol approved by the local research ethics committee. Twenty treatment resistant patients aged between 21 and 65 and fulfilling DSM IV (American Psychiaric Association, 1994) criteria for major depressive disorder (chronic) were recruited from general adult in-patient units and from out-patient clinics in Lothian. Patients also fulfilled Research Diagnostic Criteria for a primary major depressive disorder. Chronicity was defined by a diagnosis of major depressive episode (DSM IV) lasting for two or more continuous years (American Psychiatric Association, 1994). Treatment resistance was assumed if patients did not respond to at least two treatments from four different pharmacological regimes employed for at least four weeks:

1. ≥ 150mg of imipramine or an equivalent tricyclic antidepressant.
2. ≥ 60mg of phenelzine or an equivalent monoamine oxidase inhibitor.
3. ≥ 40mg of fluoxetine or an equivalent selective serotonin reuptake inhibitor.
4. ≥ 6 treatments with ECT, with seizures > 20 seconds each.

In reality, all patients far exceeded the minimum criteria for treatment resistance, many having been on multiple and/or combination treatments (appendix 5.1). All patients were on a stable medication for at least two weeks prior to the study, as it was not possible to study patients medication free. Patients had not received ECT for at least three months. Twelve patients had required at least one psychiatric admission.

Twenty patients who had recovered from depression previously fulfilling DSM IV criteria for a major depressive disorder (16 requiring inpatient treatment), and twenty normal healthy volunteers were also examined. Volunteers were recruited from the paramedical and administrative staff from the hospital, and from the community through infomal contact. Subjects from both these groups were individually matched for age, sex, intelligence and years of education with the CTRD patients. Patients with recovered depression were matched for age of onset, for onset of the index episode and for total number of depressive episodes, with the CTRD group. Recovery was defined as scoring five or less on the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) for at least three months prior to the study. Recovered patients were either on a stable medication (n=9) for at least two weeks prior to the study, or were

medication free (n=11).

Healthy volunteers had no lifetime history of significant psychiatric illness, using the SADS-L interview schedule (Endicott & Spitzer, 1978). Exclusion criteria were previous manic episodes, organic cerebral pathology, significant alcohol or substance misuse, head injury associated with significant loss of consciousness, or concurrent use of exogenous steroids.

5.2.2 Neuropsychological and clinical assessment

All subjects were interviewed using the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) (Endicott & Spitzer, 1978). All available casenotes were reviewed in detail, providing RDC diagnoses and allowing lifetime histories of psychiatric illness to be determined. Treatment and illness histories were re-constructed from casenotes and from interview, allowing an estimation of lifetime illness duration, age of onset and age at onset of last episode. The number of hospitalisations, cumulative length of psychiatric hospitalisation and cumulative number of ECT treatments were ascertained from case notes and were used as indices of cumulative illness severity (Appendix 5.1). The presence of specific psychotic symptoms (delusions or hallucinations) through the illness history was noted.

All subjects underwent neuropsychological and clinical testing in a standardised environment, within a two day period. Symptom severity was measured using the HRSD (Hamilton, 1960), the severity of psychomotor retardation using the observer rated Widlöcher scale (Widlöcher, 1983) and cerebral dominance using a handedness scale(Annett, 1970). Subjects also performed the National Adult Reading Test-Revised(Nelson & Willison, 1991), to estimate pre-morbid IQ, and a battery of neuropsychological tests described in the next chapter.

5.2.3 MR image acquisition and analysis

All subjects were scanned within one week of the clinical assessment. MR images were acquired on a 1.0 Tesla Siemens Magnetrom SPE system, with subjects undergoing a magnetisation prepared rapid acquisition graded echo (MPRAGE) sequence, acquired perpendicular to the anterior-to-posterior commissure (AC-PC) line. This sequence produces high resolution images with good contrast between white and grey matter (TR = 10ms, TD = 500ms, TI = 200ms, flip angle = 12 degrees, block size = 240mm, 128 contiguous slices with an effective slice thickness of 1.875mm). Image analysis was performed on a SPARC workstation (Sun Microsystems Europe Inc.) using

ANALYZE (CNS Software), and SPM'96 for spatial normalisation and statistical parametric mapping (Friston *et al*, 1995a; Friston *et al*, 1995b) running in MATLAB (The Mathworks Inc.).

In ANALYZE, images were first corrected for field inhomogeneities with a phantom image using image algebra, then converted to 8-bit images and flipped to reverse right and left to comply with the neurological convention. Within the SPM'96 software, images were first spatially normalised into standard space (Talairach *et al*, 1988) and then segmented into grey matter, white matter, cerebro-spinal fluid and skull/ scalp compartments, using an automated and operator independent process. Spatial normalisation involved reading image data in coronal orientation and linearly deforming them using a 12-point affine transformation to fit a T1-weighted template image which included skull and scalp. Nearest neighbour interpolation was used to preserve tissue type boundaries and the original intensity spectrum of the image. The normalised image has a voxel resolution of 1 x 1 x 2mm. Images were then segmented using a modified clustering algorithm based on the maximum likelihood "mixture model" (Hartigan, 1975) which allows classification of tissue type, as well as tissue density. The algorithm uses a combination of

the underlying multinormal distribution of T1 relaxation times, and a series of a priori probability images for each tissue type, where each voxel represents the prior probability of tissue at a location belonging to a particular compartment. The multinormal distribution reflects the distinct T1 intensity clusters from different tissue types. The essential assumption is that the range of T1 relaxation times reflect different tissue types and, within each distribution, different tissue densities. A priori segmented probability images provide approximate spatial distributions of different tissue types. These were derived from averaging the spatially transformed segmented images of grey, white matter and CSF from MRIs of healthy volunteers. The intensity distribution of the probability image ranges between 0 and 1. The algorithm is iterative and has the effect of biasing voxel classification towards the a priori distribution (Appendix 5.2). Prior to statistical comparison, the spatially normalised segments were smoothed with a 12mm FWHM isotropic Gaussian kernel to remove variation due to individual differences in sulcal and gyral patterns. The segmentation procedure used in this study is more sophisticated than the method previously applied by Wright et al (Wright *et al*, 1995). Tissues are classified having continuous values between 0 and 1 based on

probability, whereas the earlier technique classified tissue only as 0 or 1, in binary fashion. In addition, by smoothing the data, the partial volume effect is used to convert differences in the amount of grey matter locally into differences in intensity.

5.2.4 Dexamethasone Suppression Test

A dexamethasone suppression test was given to all subjects within the week after all clinical, and neuropsychological testing and imaging were completed. Dexamethasone (1mg) was taken at 10 pm, two blood samples were collected at 9.30 am and 4 pm the next day. An indwelling cannula was inserted into a forearm vein thirty minutes before the first sample, and was removed after the last sample. Samples were immediately centrifuged and the serum promptly frozen and stored at -400C. Total plasma cortisol concentrations were determined by RIA using a modification of the method of Seth and Brown (Seth & Brown, 1978), as described by Christie et al (Christie *et al*, 1986). All samples were measured in the same assay. The sensitivity of the assay was 16 nmol/l. The intra-assay coefficient of variance of a low quality sample (150 nmol/l) was 6.1%, of a high quality sample (400nmol/l) was 8.9%.

5.2.5 Statistical comparison

An ANCOVA model was applied which removed global tissue density for each subject. This normalises the transformed and segmented brain image to the same total amount of tissue, whilst preserving regional differences in tissue density. Age-effects were also removed by ANCOVA. Differences between groups were displayed as statistical parametric maps (SPMs), with a threshold probability of 1%. Statistical clusters were projected on to a T1-weighted MRI template to facilitate interpretation of the results. Corrected probability values were computed which took into account the whole volume examined, the smoothness of the data, the size of the cluster with $p < 0.01$, and the peak effect (Z-value). Group demographic and clinical data were compared using univariate ANOVA and post-hoc t-tests to identify specific group differences. Non-continuous variables were compared using the Kruskal-Wallis, Mann-Whitney U and chi-squared tests, as appropriate. Spearman non-parametric correlations were also used, as appropriate. These latter statistics were computed using SPSS version 4.0 for the Macintosh.

5.3 RESULTS

5.3.1 Comparison of clinical data.

The three groups did not statistically differ in age, sex, cerebral hemispheric laterality, years of education, estimated premorbid IQ and for the total number of years smoking (table 5.1), although there was a tendency for the CTRD patients to have a lower NART IQ particularly in comparison to control subjects, and to be right-lateralised to a lesser degree. The mean age of onset of the first and most recent, and lifetime number of depressive episodes did not differ between the treatment resistant and recovered groups. The CTRD group had a longer current episode and total duration of illness, and had greater number and longer total hospitalisations (table 5.1, appendix 5.1).

All CTRD patients were taking antidepressant drugs. Additionally, twelve patients took regular neuroleptic medication, five lithium and three benzodiazepines. Eleven of the RD group were medication free. Nine of the recovered patients were prescribed antidepressants, one also received neuroleptics and one lithium.

Both the CTRD and RD patients had, or previously had melancholic depressive episodes- the CTRD group had endogenous/ melancholic symptoms as measured by the Newcastle scale (Carney *et al*, 1965) and fulfilled the DSM-IV criteria for a

Table 5.1: Comparison of 20 CTRD patients, RD patients and controls on clinical and demographic variables.

	CTRD group (n=20)	RD group (n=20)	Controls (n=20)	F2, 57 probability (t-test for two group comparisons)	Post- hoc t-test
Mean age (SD)	48.9 (9.8)	47.7 (9.9)	49.3 (11.8)	0.89	
Male: female ratio	13:7	13:7	13:7		
Handedness score (SD)	13 (16)	16 (13)	19 (5)	0.27	
Years Education (SD)	11.7 (2.9)	13.4 (3.4)	13.5 (2.9)	0.12	
Nart IQ (SD)	**107 (12.7)**	**113 (10.2)**	**115 (8.7)**	**0.06**	**CTRD=RD CTRD<C**
HRSD score (SD)	**20.6 (5.3)**	**2.6 (1.7)**	**0.2 (0.7)**	**<0.0001**	**CTRD>RD>C**
Widlocher score (SD)	**26.1 (8.6)**	**2.2 (3.6)**	**0.3 (0.7)**	**<0.0001**	**CTRD>RD>C**
Total years smoking (SD)	20 (13.6)	12 (13.7)	17 (3.7)	0.14	
Age onset first episode (SD)	38.9 (13.5)	38.2 (10.1)		0.89	
Age onset last episode (SD)	45.8 (10.1)	44.8 (9.8)		0.76	
Total number of episodes (SD)	2.2 (1.4)	2.5 (1.9)		0.52	
Longest duration of episode in weeks (SD)	197 (125)	46 (36)		<0.001	
Lifetime total illness duration in weeks (SD)	263 (133)	76 (58)		<0.001	
Total number of hospitalisation (SD)	3.8 (5.3)	1.3 (1.2)		2.06 (0.05)	

depressive episode with melancholic features (American Psychiaric Association, 1994). The RD patients also previously fulfilled DSM-IV criteria for having depressive episodes with melancholic features.

The CTRD patients had moderately severe depressive symptoms (17-item HRSD, mean: 20.6, sd: 5.3, range: 10 to 30) and moderately severely psychomotor retardation (table 5.1). Although not clinically depressed, scoring five or less on the HRSD, and not fulfilling the criteria for a major depressive episode, the recovered depressed patients had significantly more depressive symptoms and more clinically observed motor retardation than controls (table 5.1). This was not a medication effect: there was no difference in either HRSD score (3.3, (SD= 1.3) vs 2.0, (SD= 1.8); t= -1.82, p=0.9) or Widlocher score (2.1, (2.7) vs 2.4, (4.3); t= 0.16, p= 0.88) between medicated (n=9) and medication free (n=11) recovered patients.

Although not significant. the CTRD patients had a tendency to have been smokers for longer than both controls (mean=20.4 years (SD= 13.6) vs 12.1 (16.6); t= 1.72, p=0.09) and the RD patients (20.4 (13.6) vs 12.3 (13.7); t= 1.85, p= 0.07).

Post-dexamethasone morning and afternoon cortisol values did not differ between the three groups. Median values for chronic, recovered patients and controls were 16.0, 21.6, and 24.0

nmol/l (c2 = 4.1, p=0.13, corrected for ties) and 16.5, 21.1, and 23.4 nmol/l (c2 = 0.3, p=0.85), respectively. Values ranged between 16.0 and 44.6 nmol/l (0.58 - 1.61 mg/dl) in the morning, and 16.0 and 82.4 nmol/l (0.58 - 2.97 mg/dl) in the afternoon, i.e. all subjects were suppressors (Carroll *et al*, 1981).

5.3.2 Regional differences in grey and white matter, and CSF

A three group comparison of increases and decreases in each of the three tissue compartments yielding eighteen SPMs. There were no significant differences in any of the tissue compartments between the recovered patients and controls. Tables 5.2, 5.3 and 5.4 show that only the CTRD group had changes in all three tissue compartments in comparison to the recovered and control group. Since there was almost exact convergence of the areas of difference with CTRD patients, and as there was no significant difference between the recovered group and controls in any of the three tissue compartments, the recovered and control groups were combined and jointly compared against the remaining twenty images from the chronically depressed patients. The combination of resultant SPMs from this comparison is illustrated in Figure 5.1.

5.3.2.1 Limbic changes (table 5.2)

The CTRD group had reduced bilateral hippocampal and parahippocampal grey matter density particularly anteriorly and more marked on the left. There was an overlapping increase in white matter density over bilateral anterior hippocampi and medial temporal lobe. Similarly, there was reduced grey matter density in the left Broadman area 24 (rostral anterior cingulate) in only the CTRD patients, with an associated increase in white matter density in the same area, extending into the anterior corpus callosum. Finally, right basal ganglia tissue density was reduced, with a corresponding increase in the overlying right lateral ventricular CSF in only the CTRD group, suggesting an anatomical volume reduction in right striatum.

5.3.2.2 Cortical and other changes (tables 5.3 and 5.4)

There were large grey matter density reductions in the left superior and medial temporal gyri with white matter density reductions in the right medial temporal gyrus. The right superior frontal gyrus had small reductions in grey matter density in the CTRD group, with the adjacent medial frontal gyrus having grey matter increases. There were large

Table 5.2: Changes in limbic grey and white matter, and CSF in CTRD patients compared to two other groups

Chronic vs controls			Chronic vs recovered			Chronic vs recovered+controls		
Limbic regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)	Limbic regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)	Limbic regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)
↓ left hippocampus (GM)	-29, -18, -16 (<0.001)	2282 (0.004)	↓ left hippocampus (GM)	-25, -30, -8 (<0.001)	2780 (0.002)	↓ left hippocampus (GM)	-29, -27, -12 (<0.001)	3524 (0.001)
			↓ left parahippocampal (GM)	-32, -20, -20 (<0.001)			-30, -18, -18 (<0.001)	
							-36, -15, -26 (<0.001)	
↑ left hippocampus (WM)	-29, -24, -14 (0.002)	531 (0.173)	↑ left hippocampus (WM)	-29, -24, -14 (<0.001)	1271 (0.043)	↑ left hippocampus (WM)	-29, -24, -14 (<0.001)	1466 (0.03)
↑ left fusiform (WM)	-41, -38, -18 (0.002)		↑ left parahippocampal (WM)	-27, -31, -10 (<0.001)			-38, -22, -18 (<0.001)	
	-41, -28, -18 (0.002)						-37, -10, -28 (<0.001)	
↓ right hippocampus (GM)	31, -25, -12 (0.002)	700 (0.078)	↓ right hippocampus (GM)	29, -29, -12 (0.001)	683 (0.081)	↓ right hippocampus (GM)	29, -29, -12 (<0.001)	1200 (0.03)
				30, -21, -8 (0.001)			26, -20, -14 (0.001)	
				17, -11, -16 (0.004)			20, -14, -16 (0.001)	
↑ right hippocampus (WM)	28, -20, -14 (0.003)	1106 (0.057)	↑ right hippocampus (WM)	30, -29, -12 (0.002)	341 (0.271)	↑ right hippocampus (WM)	31, -29, -12 (<0.001)	1219 (0.05)
							17, -14, -18 (<0.001)	
↓ L. ant. cingulate (BA24) GM	-8, 25, -6 (0.003)	564 (0.1)	↓ L. ant cingulate (BA24) GM	-9, 23, -6 (0.001)	326 (0.216)	↓ L. ant cingulate (BA24) GM	-8, 23 ,-6 (0.001)	683 (0.08)
↓ L. fronto-medial GM	-9, 36, -14 (0.001)			-18, 20, -2 (<0.001)			-18, 20, -2 (<0.001)	
						↓ R. ant cingultae (BA24) GM	5, 19, -4 (0.002)	
↑ L. ant. cingulate (BA24) WM	-7, 30, -6 (0.005)	325 (0.283)	↑ L. corpus callosum WM	-12, 32, 8 (<0.001)	1933 (0.016)	↑ L. ant cinglate (BA24) WM	-9, 31, -4 (0.003)	2374 (0.009)
			↑ R. corpus callosum WM	1, 26, 8 (0.001)		↑ L. corpus callosum WM	-14, 33 ,8 (<0.001)	
				8, 27, 4 (0.001)			-22, 32, 4 (0.001)	
↓ R. putamen (WM)	16, 4, 6 (<0.001)	1149 (0.05)	↓ R. putamen (WM)	15, 5, 2 (<0.001)	589 (0.153)	↓ R. putamen (WM)	16, 6, 4 (<0.001)	1333 (0.04)
↓ R. Lat Ventricle (CSF)	11, 3, 8 (0.003)	687 (0.22)				↓ R. Lat Ventricle (CSF)	10, 4, 4 (0.001)	1180 (0.1)
	6, 9, 2 (0.004)							

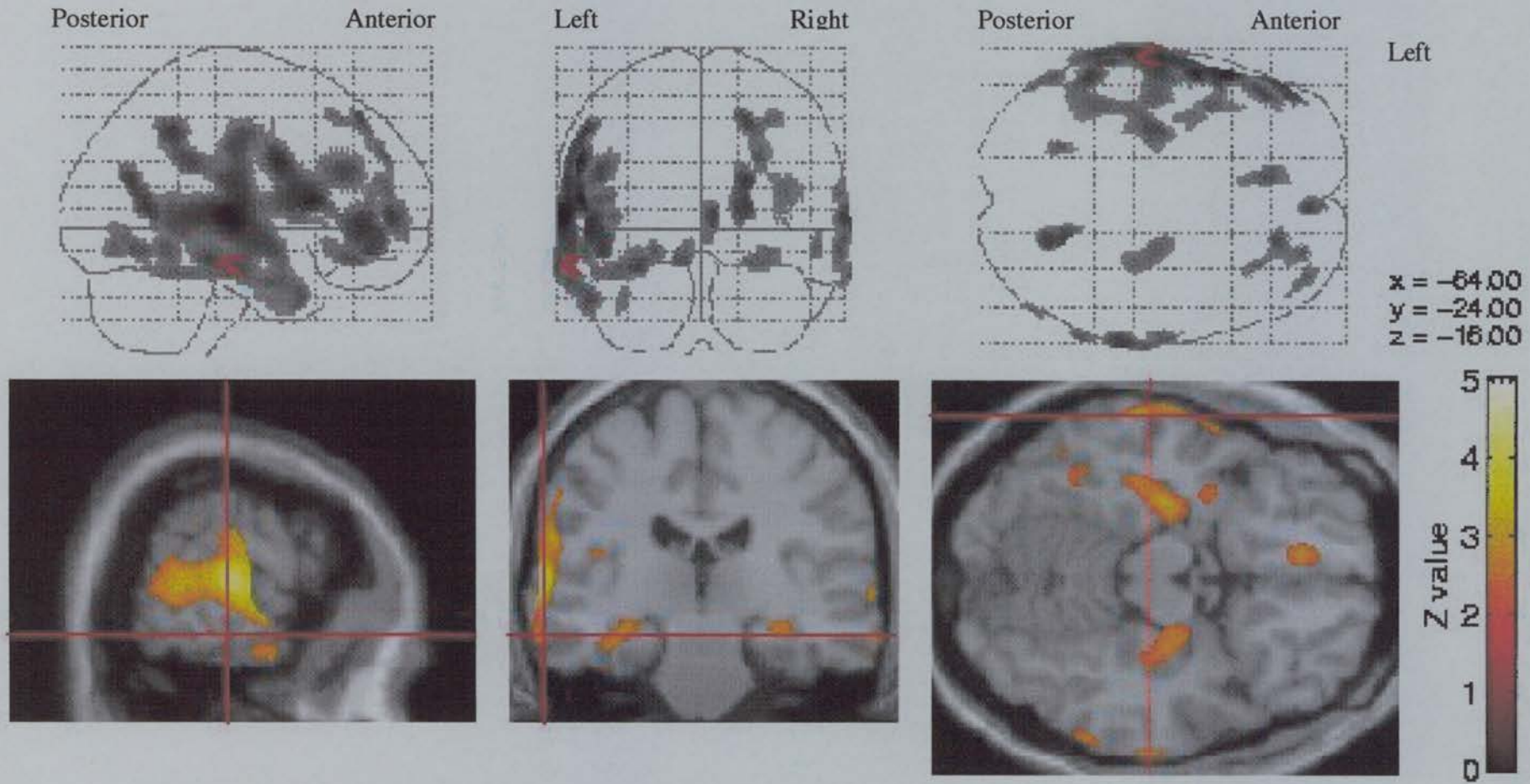
Table 5.3: Changes in neocortical grey and white matter, and CSF in CTRD patients compared to two other groups

Chronic	vs controls		Chronic	vs recovered		Chronic vs	recovered+controls	
Cortical regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)	Cortical regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)	Cortical regions	Co-ordinates of peak voxels (uncorrected p)	Size of cluster in voxels (uncorrected p)
↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM	21, 40, 50 (p<0.001) 26, 52, 32 (p=0.001) 32, 31, 50 (p=0.001)	371 (0.188)	↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM	22, 43, 56 (p<0.001) 34, 26, 52 (p=0.001) 41, 21, 50 (p=0.001)	667 (0.085)	↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM ↓ R. sup. front gyrus GM	22, 41, 48 (<0.001) 34, 26, 52 (<0.001) 26, 52, 32 (<0.001)	1030 (0.04)
↑ R Inf. Front (BA 10) GM ↑ R Med. Front (BA 40) GM	38, 49, 0 (0.008) 38, 40, 18 (0.001)	365, (0.192)	↑ R. inf. frontal (BA10) GM ↑ R. inf. frontal (BA10) GM	37, 45, 12 (0.001) 30, 51, 12 (0.003)	318 (0.22)	↑ R. med frontal (BA10) GM ↑ R. med frontal (BA8) GM ↑ R. med frontal (BA40) GM	38, 43, 12 (<0.001) 33, 25, 38 (0.001) 39, 34, 28 (0.001)	923 (0.05)
↓ R. med. frontal WM ↓ R. med. frontal WM ↓ R. sup. frontal WM	35, 44, 4 (<0.001) 37, 40, 16(<0.001) 18, 50, 24(<0.001)	2751 (0.005)	↓ R. med. frontal WM ↓ R. sup. frontal WM ↓ R. sup. frontal WM	31, 50, 6 (<0.001) 14, 57, 12 (<0.001) 18, 48, 24 (<0.001)	4616 (0.001)	↓ R. med. frontal WM ↓ R. med. frontal WM ↓ R. sup. frontal WM	31, 50, 4 (<0.001) 36, 41, 10 (<0.001) 18, 50, 24 (<0.001)	5374 (<0.001)
↑ R Frontal CSF	27, 54, 32 (<0.001) 42, 47, 24 (<0.001) 21, 41, 48 (<0.001)	4299 (0.006)	↑ R Frontal CSF	42, 30, 42 (<0.001) 40, 49, 24 (<0.001) 19, 44, 42 (<0.001)	7604 (0.001)	↑ R Frontal CSF	28, 53, 32 (<0.001) 41, 48, 24 (<0.001) 19, 42, 44 (<0.001)	8542 (<0.001)
↓ R. med. temporal WM ↓ R. med. temporal WM ↓ R. sup. temporal WM	46, -15, -12 (<0.001) 47, -4, -24 (0.001) 48, -32, 8 (0.001)	1900 (0.017)	↓ R. med. temporal WM ↓ R. med. temporal WM	45, -15, -16 (0.002) 43, -1, -26 (0.001)	562 (0.162)	↓ R. med. temporal WM ↓ R. med. temporal WM ↓ R. sup. temporal WM	45, -15, -14 (<0.001) 46, -4, -24 (<0.001) 45, -32, 6 (0.001)	1828 (0.02)
↓ L. Sup. Temp. GM ↓L. Inf. Frontal GM ↓L. precent. gyrus GM	-64, -23, 6 (<0.001) -55, 14, 14 (<0.001) -56, 1, 32 (<0.001)	9806 (<0.001)	↓ L. Sup. Temp. GM ↓ L. Med. Temp. GM ↓ L. precent. gyrus GM	-64, -23, 8 (<0.001) -68, -28, -14 (<0.001) -58, -16, 38 (<0.001)	5930 (<0.001)	↓ L. Sup. Temp. GM ↓ L. Precent. Temp. GM ↓ L. precent. gyrus GM	-64, -23, 8 (<0.001) -56, 1, 32 (<0.001) -59, -17, 36 (<0.001)	11,897 (<0.001)
↓ L. med/sup front (BA10) WM	-30, 43, 8 (0.004)	444 (0.2)	↓ L. med/sup front (BA10) WM ↓ L. med/sup front (BA10) WM ↓ L. med/sup front (BA10) WM	-23, 48, 4 (<0.001) -28, 30, 20 (0.005) -26 37, 16 (0.007)	1445 (0.03)	↓ L. med/sup front (BA10) WM ↓ L. med/sup front (BA10) WM	-24, 46, 6 (<0.001) -26, 35, 18 (0.005)	1510 (0.03)
↑ L Frontal CSF	-43, 59, 18 (<0.001) -44, 41, 36 (0.001) -46, 51, 32 (0.002)	3023 (0.02)	↑ L Frontal CSF	--39, 53, 14 (<0.001) -8, 71, 4 (<0.001) -7, 69, 12 (<0.001)	3023 (0.02)	↑ L Frontal CSF	--39, 53, 14 (<0.001) -38, 53, 14 (<0.001) -41, 19, 54 (0.002)	5690 ((0.002)
						↑ midline prefrontal CSF	5, 68, -8 (<0.001) 9, 62, 4 (0.001) -10, 71, 2 (0.001)	2096 (0.04)

Table 5.4: Changes in grey and white matter, and CSF in other regions, in CTRD patients compared to two other groups

Chronic vs controls			Chronic vs recovered			Chronic vs recovered+controls		
Region	Co-ordinates	Size in voxels (uncorrected p)	Region	Co-ordinates	Size in voxels (uncorrected p)	Region	Co-ordinates	Size in voxels (uncorrected p)
↓ R. precuneus GM	21, -67, 22 (<0.001)	758 (0.068)				↓ R. precuneus GM	24, -66, 22 (<0.001)	674 (0.08)
↓ R. post cing GM	21, -60, 10 (<0.001)					↓ R. post cing GM	21, -60, 10 (<0.001)	
↑ R. precuneus WM	21, -66, 22 (<0.001)	1238 (0.046)	↑ R. precuneus WM	22, -63, 18 (0.001)	1179 (0.05)	↑ R. precuneus WM	22, -66, 22 (<0.001)	1831 (0.02)
↑ L. precuneus GM	-4, -52, 34 (<0.001)	6442 (<0.001)	↑ L. precuneus GM	-4, -53, 34 (<0.001)	16, 521 (<0.001)	↑ L. precuneus GM	-4, -53, 34 (<0.001)	17,418 (<0.001)
↑ L. cuneus GM	-16, -86, 24 (<0.001)		↑ L. cuneus GM	-12, -89, 22 (<0.001)		↑ L. cuneus GM	-14, -88, 22 (<0.001)	
↑ L. lingual gyrus GM	-8, -72, 0 (<0.001)		↑ L. precuneus GM	-5, -73, 24 (<0.001)		↑ L. lingual gyrus GM	-8, -69, 0 (<0.001)	
↑ R. cerebellum GM	40, -45, -32 (0.001)	2787 (0.002)	↑ R. cerebellum GM	44, -58, -32 (0.002)	753 (0.07)	↑ R. cerebellum GM	49, -49, -34 (0.001)	2453 (0.003)
	21, -30, -28 (0.001)			52, -51, 34 (0.003)			42, -59, -32 (0.001)	
	29, -31, 26 (0.001)						42, -43, -32 (0.001)	
↑ L. cerebellum GM	-40, -50, -34 (0.001)	2674 (0.002)				↑ L. cerebellum GM	-41, -55, -32 (0.001)	2326 (0.004)
	-35, -43, -32 (0.001)						-18, -33, -22 (0.001)	
	-28, -27, -26 (0.001)						-59, -38, -26 (0.002)	

Figure 5.1a. Grey matter density reductions in CTRD patients compared to controls.



115

Figure 5.1b.Tissue density changes in CTRD patients compared to controls and RD superimposed on transverse sections 2mm apart..

Key-

The Z-maps of tissue changes in the CTRD group compared to the combined recovered depressed and control group have been colour coded and then superimposed on to the appropriate transverse section to facilitate interpretation.

Blue= reductions in grey matter density

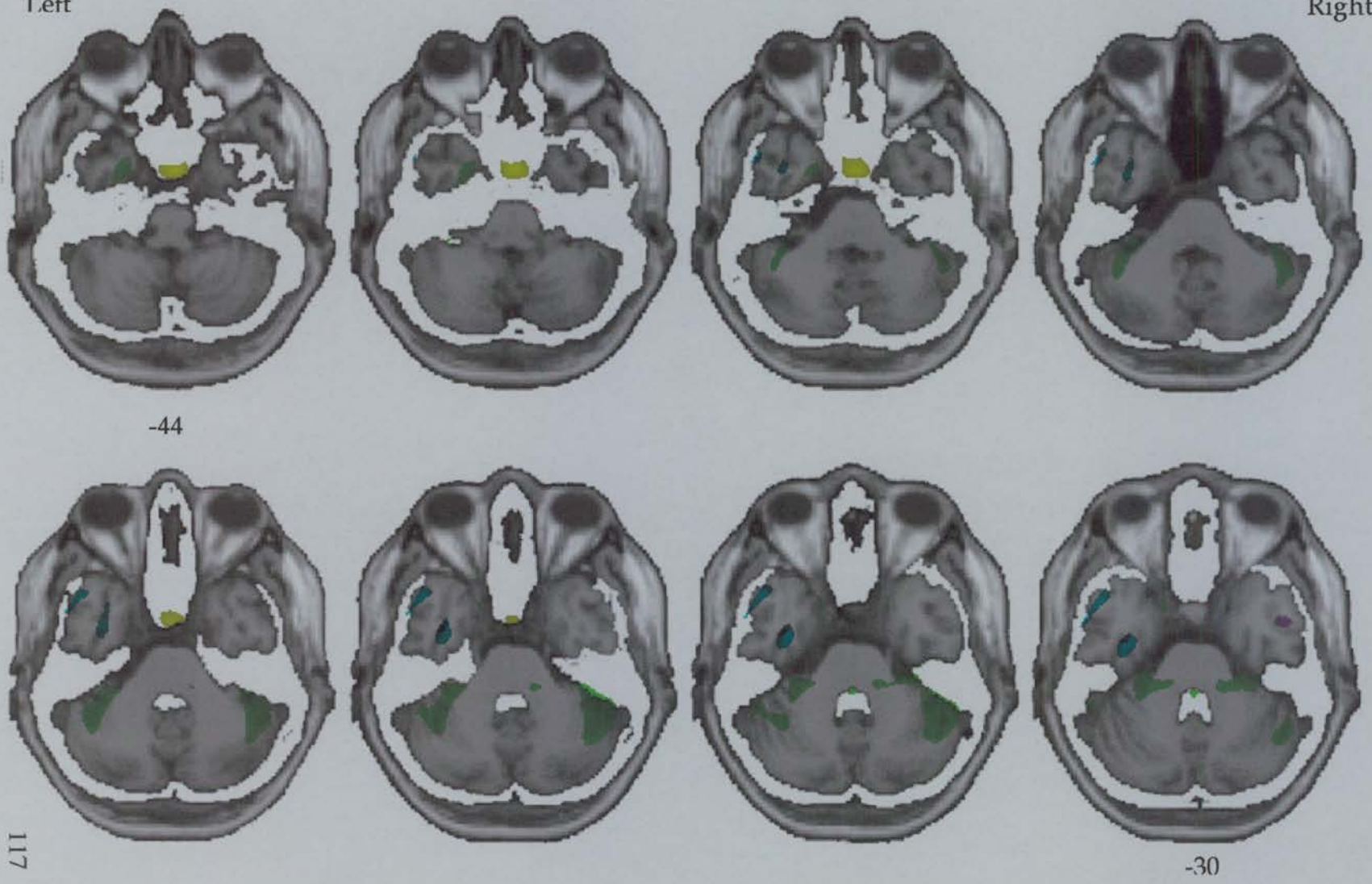
Green= increases in grey matter density

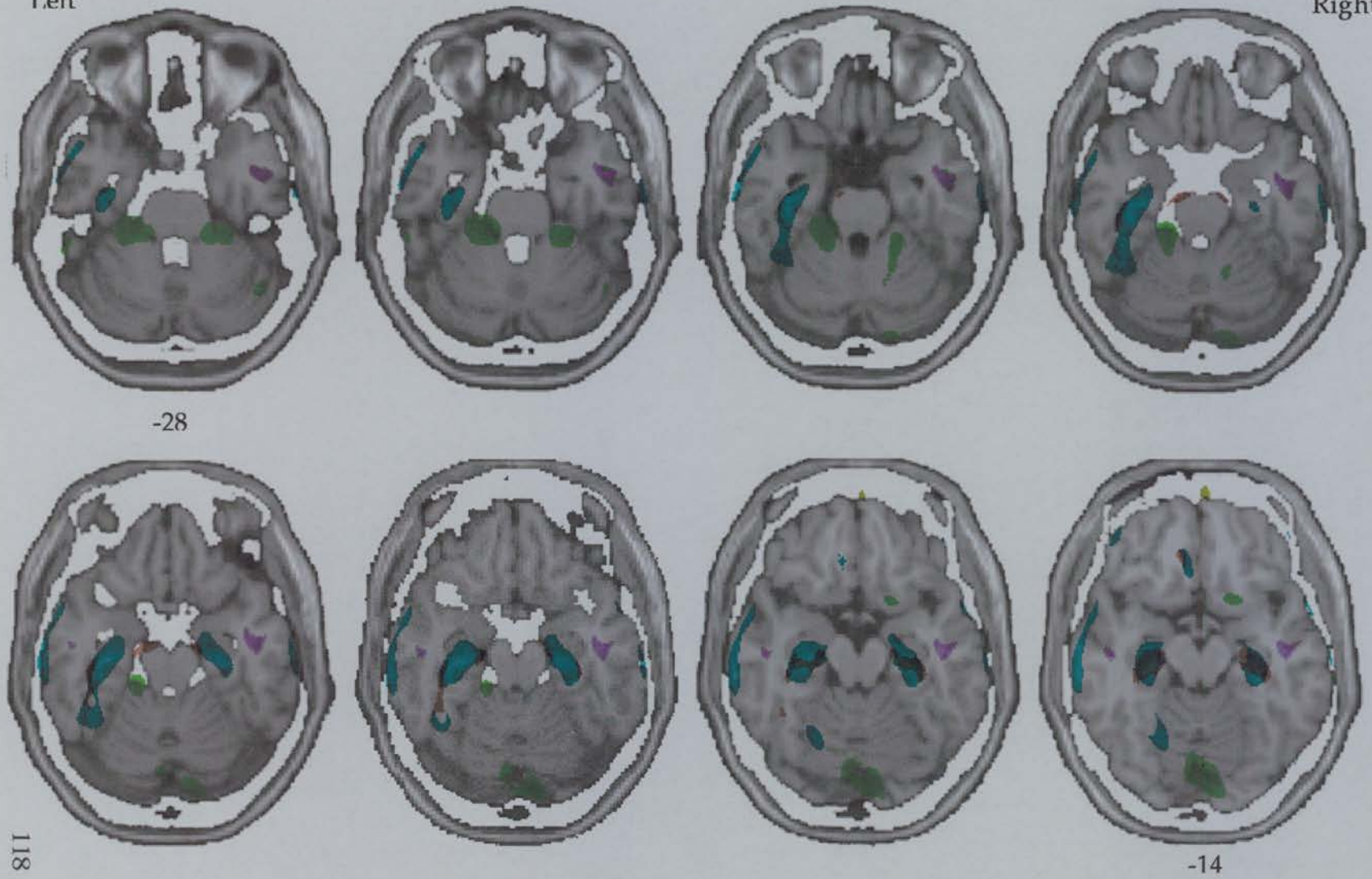
Yellow= increases in CSF

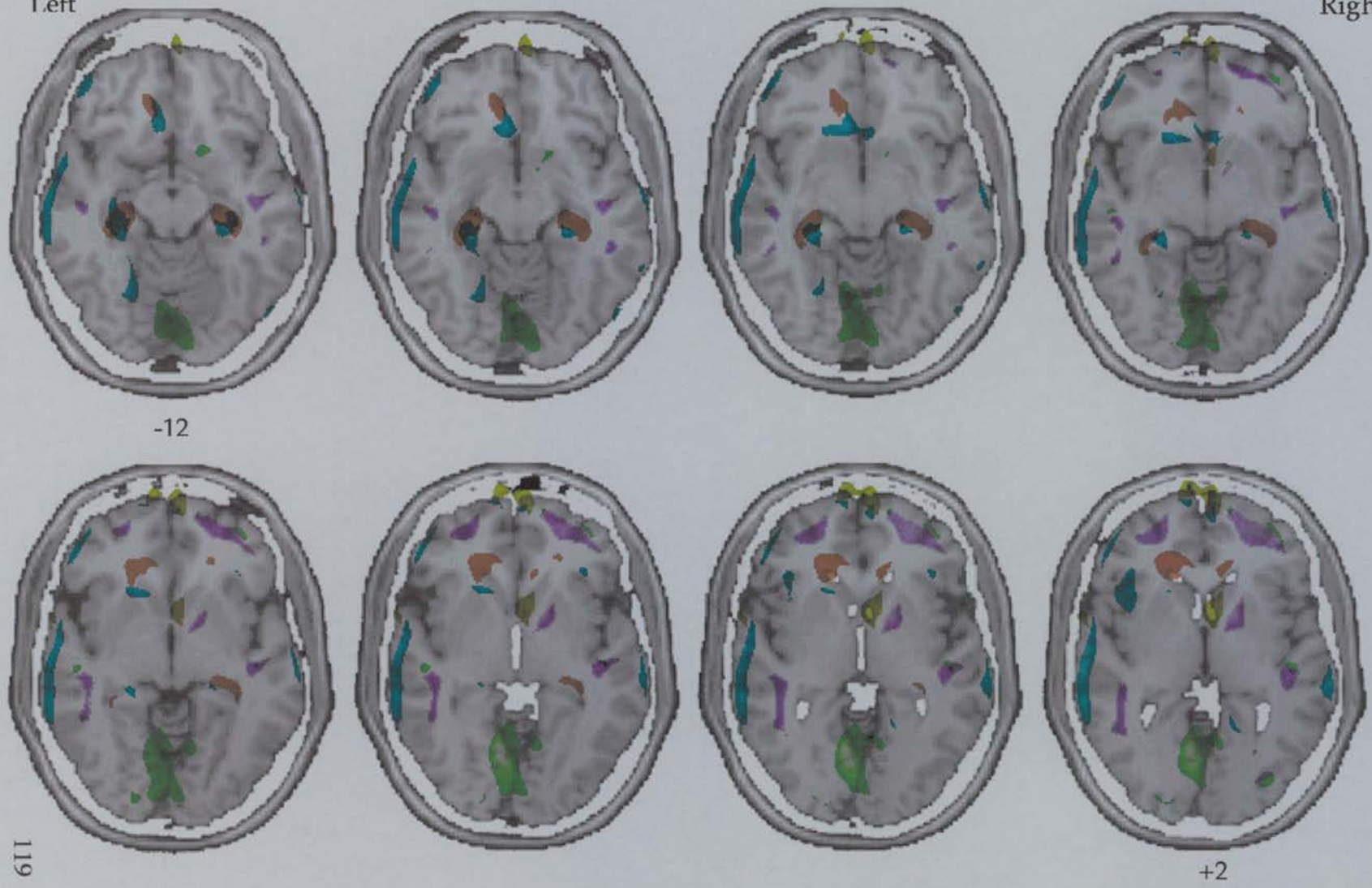
Purple= reductions in white matter density

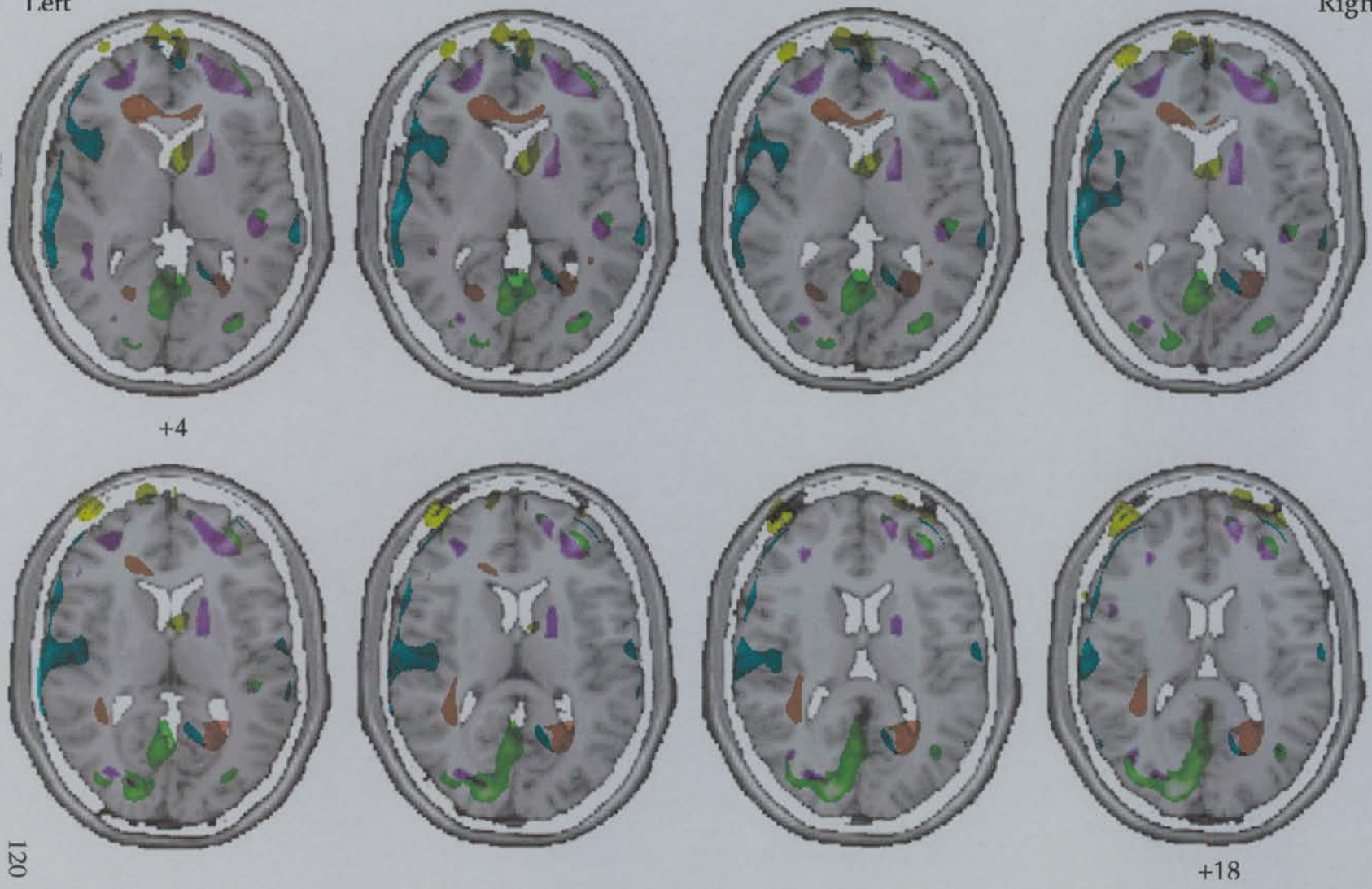
Red/ brown= increases in white matter density

Left and right orientation are indicated in the figure. Sections are taken every 2mm. The legend indicates the distance (in mm) above or below the transverse plane formed by a line passing from the anterior to posterior commisures.


Left
Right
-44
117
-30


Left
Right
-28
118
-14


Left
Right
-12
119
+2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Right
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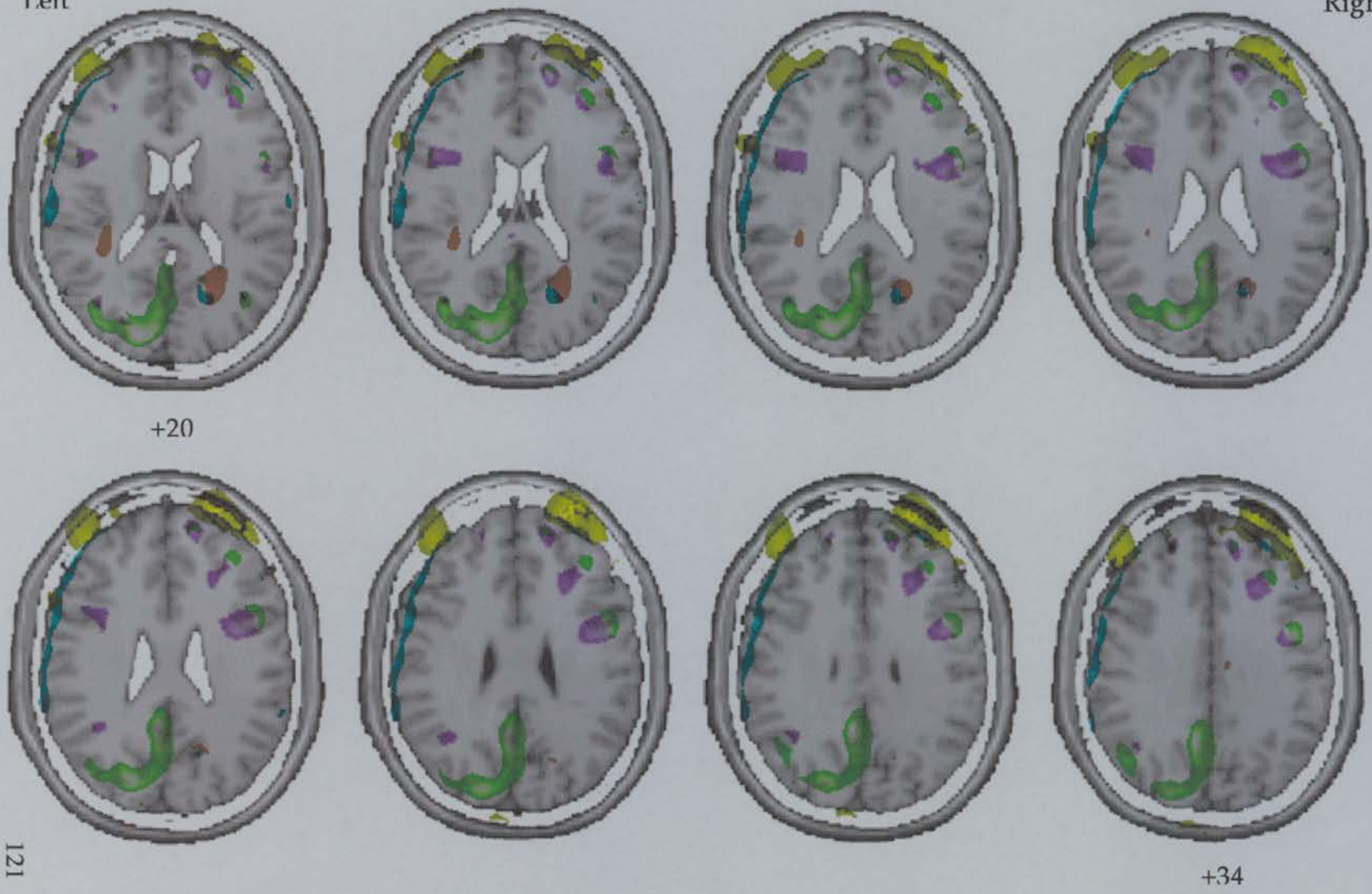
120
+18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Right
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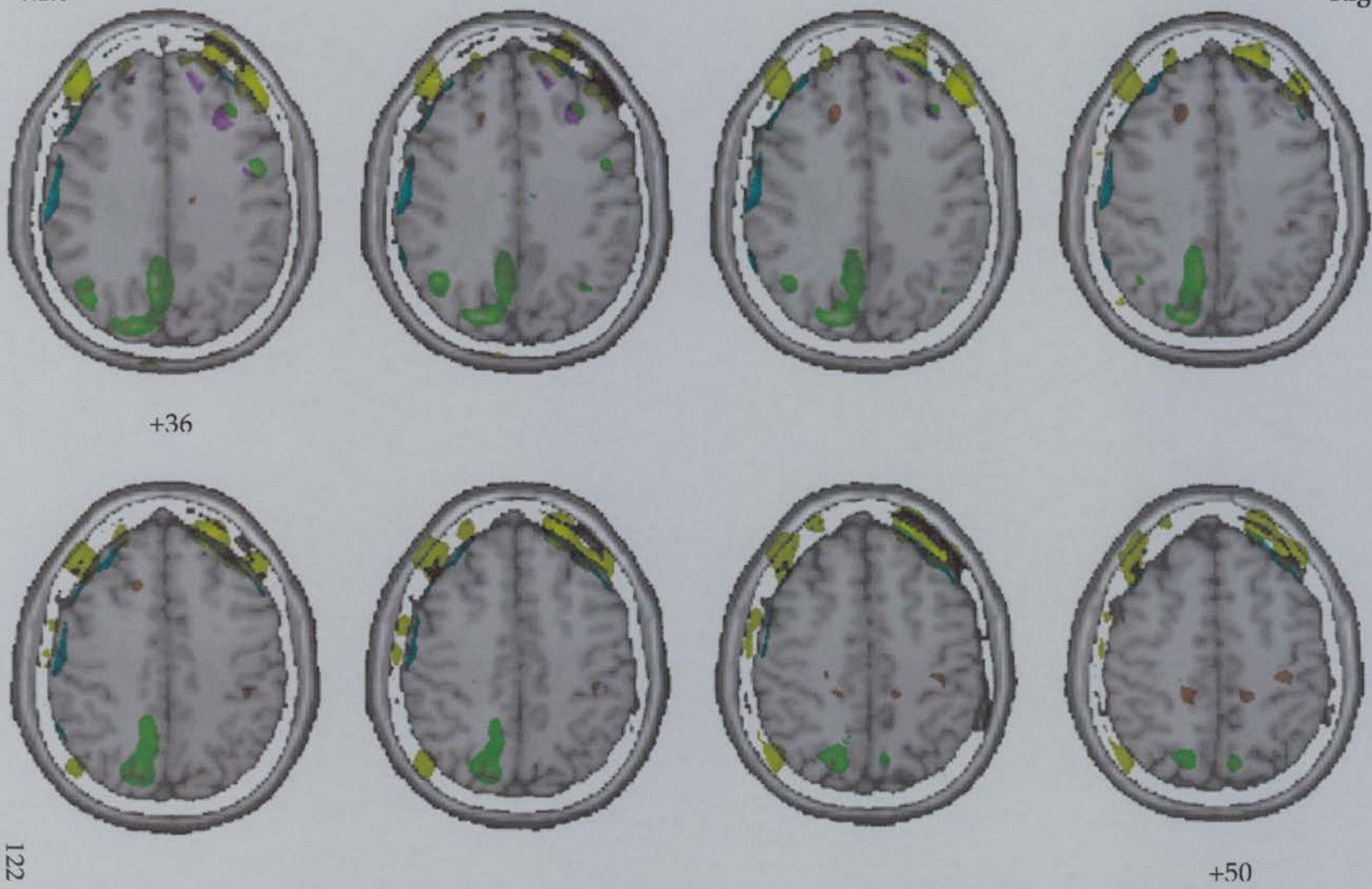
121
+34


Left
Right
+36
122
+50

reductions in white matter density in the right medial and superior frontal gyri and a corresponding large increases in CSF over the right frontal lobe, suggesting an anatomical reduction in anterior frontal lobe. The changes were less marked in the left frontal lobe- grey matter changes were not seen, there were small white matter reductions in left medial and supeior gyri, with a corresponding increase in overlying CSF. Finally, grey matter density was increased in the left cuneus, precuneus and lingual gyrus in the CTRD group, with a milder increase in bilateral cerebellum. Interestingly, grey matter decreased and white increased in the right pecuneus and posterior cingulate.

5.3.2.3 Volumetric analysis

The above results predict that volumetric reductions would be confined to right basal ganglia and right anterior (prefrontal cortex) in only the CTRD group. Appendices 5.3 and 5.4(1-5b) describes the methods and results of volumetric analysis. Volumetric analysis confirmed the prediction that CTRD patients had reduced volume of right prefrontal tissue and right caudate, particularly in comparison to controls, but also to a lesser extent in comparison to recovered patients.

5.3.3 Correlations

5.3.3.1 Correlation between clinical variables

Table 5.5 shows the Spearman correlation co-efficients between clinical variables. The number of past psychiatric hospitalisations, the cumulative duration of in-patient treatment and the cumulative number of ECT administered were closely correlated. There was a close correlation between the observed severity of psychomotor retardation (Widlocher score) and current severity of depressive symptoms (HRSD score) in both CTRD and RD groups, but not in controls. In the CTRD group, both the current severity of retardation and depression were associated with cumulative severity of illness (cumulative number of ECT). Both the Widlocher and HRSD scores had a tendency to correlate with cumulative duration of in-patient stay. In contrast, both the total duration of illness and apparent premorbid IQ did not correlate with any of the measures.

Current age and age of onset of depression were positively correlated in both the CTRD (Spearman's $\sigma = 0.57$, $p = 0.004$) and RD ($\sigma = 0.52$, $p = 0.009$) groups, suggesting the age of onset was later in older patients. In the CTRD group, age of onset positively correlated with Newcastle score and negatively with total number of episodes, suggesting onset of depression at an older age was associated with a more

Table 5.5: Spearman correlations between clinical features of illness.

	HRSD Score	No. Past psychiatric hospitalisations	Total number of ECT	Total time in hospital	Total illness duration	Premorbid IQ
Widlocher score	**0.76 (<0.001)**	0.34 (0.14)	**0.52 (0.018)**	**0.40 (0.077)**	0.12 (0.62)	0.03 (0.91)
Premorbid IQ	0.08 (0.74)	-0.17 (0.49)	-0.27 (0.26)	0.06 (0.82)	0.15 (0.54)	
Total illness duration	-0.12 (0.61)	0.40 (0.08)	0.35 (0.13)	0.34 (0.14)		
Total time in hospital	0.26 (0.26)	**0.87 (<0.001)**	**0.84 (<0.001)**			
Total number of ECT	**0.42 (0.067)**	**0.87 (<0.001)**				
No. Past psychiatric hospitalisations	0.28 (0.22)					

p- values in parentheses

melancholic type depression and fewer episodes (Table 5.6). There was no correlation, however, between current age or age of onset and number of ECT, number and duration of hospitalisations. Thus older onset patients had not recieved more or less ECT than younger patients. Current age negatively correlated with total duration of illness.

In the RD group, current age and age of onset both positively correlated with number of ECT received (Table 5.6). Age of onset negatively correlated with total illness duration and number of episodes. Thus, later onset recovered patients

Table 5.6: Correlations between age and clinical variables in the two patient groups

	CTRD group	RD group
Widlocher score	-0.15 (0.25)	0.24 (0.16)
HRSD score	0.25 (0.14)	0.28 (0.11)
Tot. Duration of illness	**-0.4 (0.039)**	0.08 (0.36)
Total number of episodes	**-0.46 (0.02)**	0.13 (0.3)
Total duration of hospitalisation	-0.35 (0.07)	0.14 (0.29)
Total lifetime ECT	-0.31 (0.09)	**0.52 (0.009)**
No. of previous psychiatric hospitalisations	-0.3 (0.099)	0.18 (0.22)

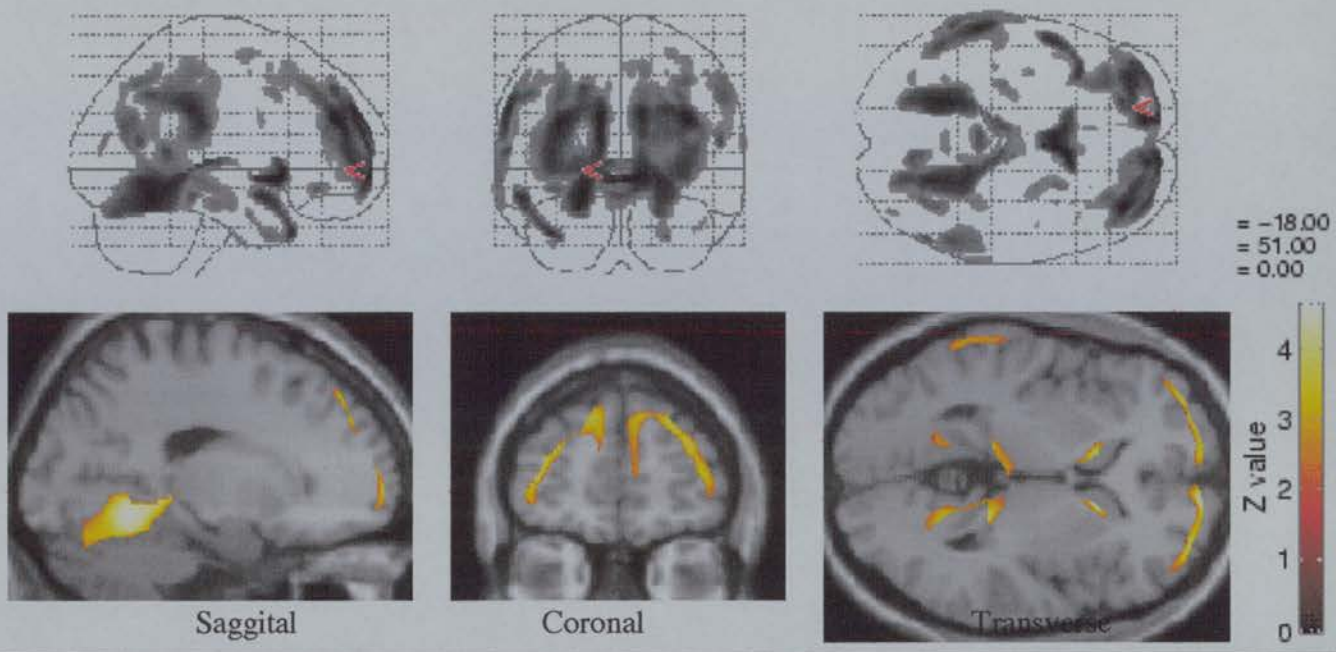
had received more ECT, suffered depression for shorter time and had fewer episodes than younger recovered patients. There were no other correlations with age of onset. Finally, there was no correlation between clinically measured retardation (Widlocher score) and age or age of onset in either of the patient groups.

5.3.3.2 Grey density correlations with clinical features

A. Cumulative illness severity

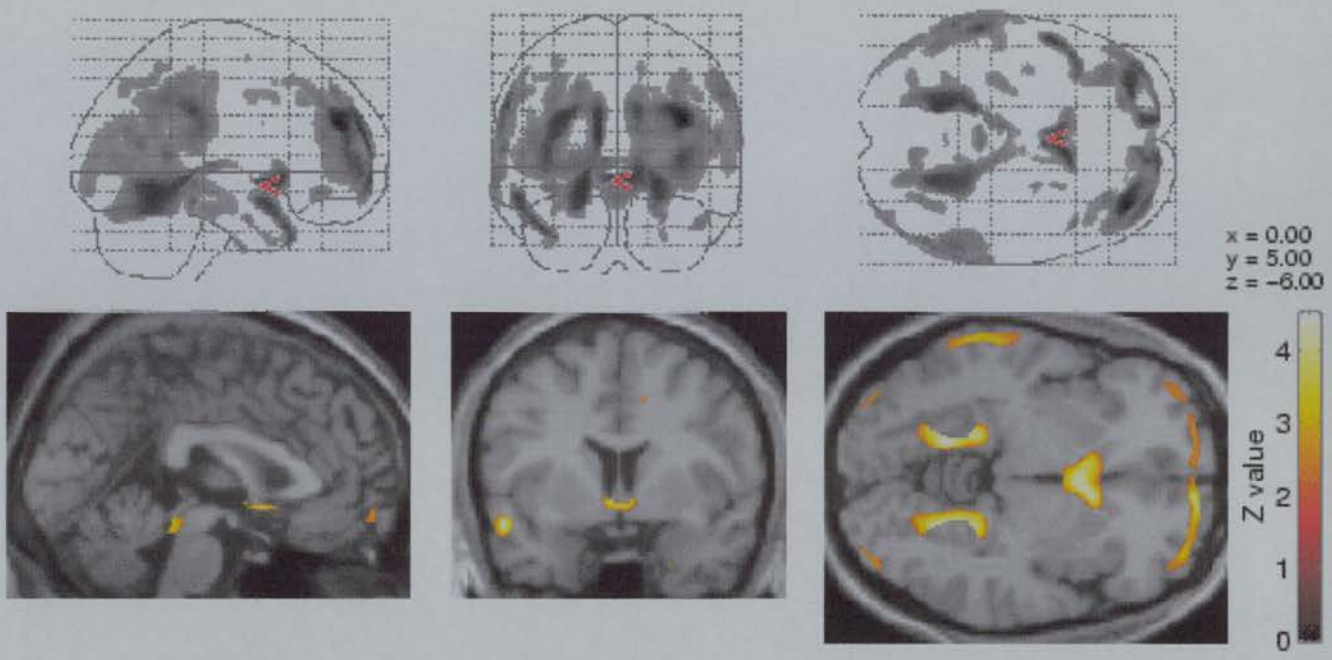
As the total number of psychiatric hospitalisations, the cumulative duration of hospitalisations and the cumulative number of

Figure 5.2. Negative correlations between grey density and total number of ECT in CTRD patients



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
11, 15, -2 (4.99)	<0.001 (0.006)	R. caudate	1326	0.022 (0.032)
4, 8, -6 (4.80)	<0.001 (0.014)	R. caudate		
-13, 14, 2 (3.91)	<0.001 (0.36)	L. caudate		
-37, 45, 26 (4.88)	<0.001 (0.01)	L. medial frontal (9)	10195	<0.001 (0.002)
-10, 55, 30 (4.85)	<0.001 (0.01)	L. superior frontal (9)		
-33, 48, 24 (4.69)	<0.001 (0.02)	L. medial frontal (9/ 10)		
-20, -57, -14 (4.80)	<0.001 (0.01)	L. cerebellum	10573	<0.001 (0.002)
23, -61, -6 (4.55)	<0.001 (0.04)	R. cerebellum		
24, -42, -8 (4.36)	0.001 (0.08)	R. cerebellum		
-60, -34, 34 (4.54)	<0.001 (0.04)	L. inferior parietal (40)	4042	<0.001 (0.034)
-62, -29, 26 (4.14)	<0.001 (0.18)	L. inferior parietal (40)		
-61, -48, 10 (3.68)	<0.001 (0.62)	L superior temporal (21)		
-35, 19, -36 (4.45)	<0.001 (0.06)	L temporal pole (38)	1023	0.04 (0.12)
-53, 6, -16 (4.44)	<0.001 (0.06)	L. superior temporal (38)		
-44, 17, -28 (3.65)	<0.001 (0.66)	L. superior temporal (38)		
54, -62, 16 (3.68)	<0.001 (0.62)	R medial temporal (39)	1426	0.018 (0.42)
56, -48, 40 (3.49)	<0.001 (0.82)	R. inferior parietal (40)		
56, -38, 46 (3.08)	0.001 (0.99)	R. inferior parietal (40)		

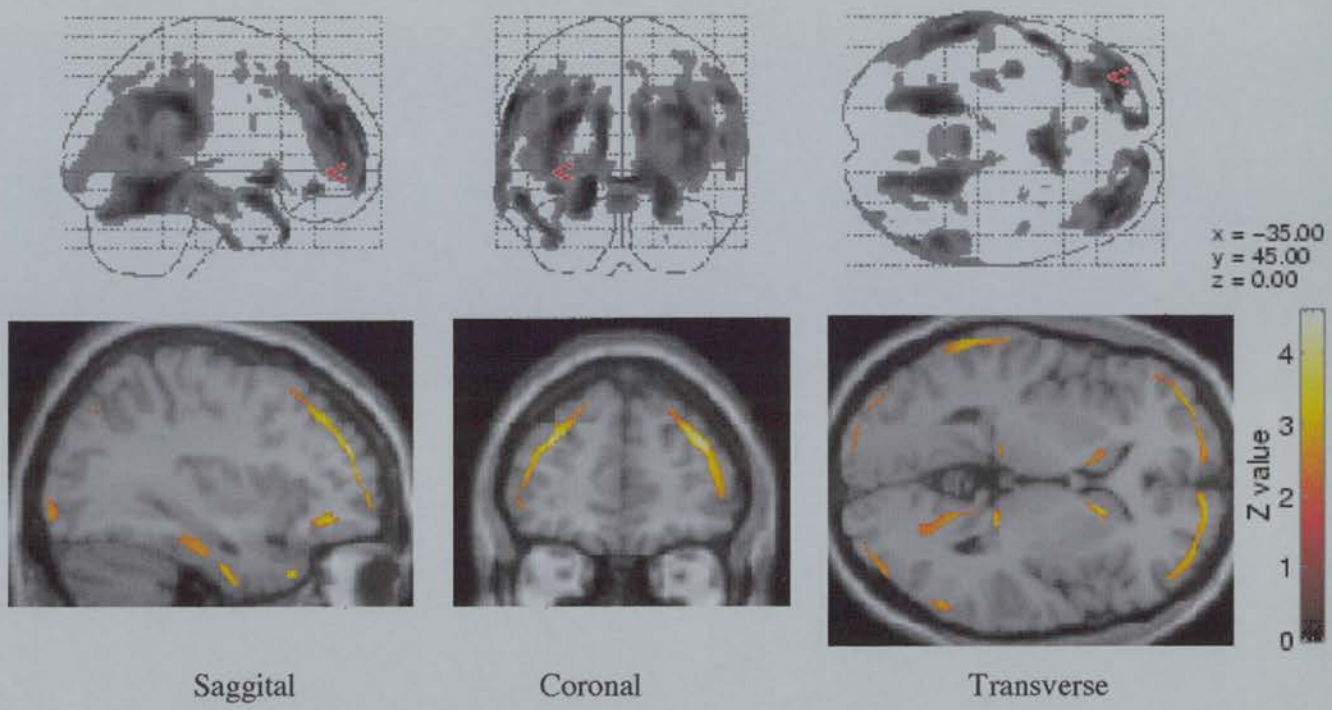
Figure 5.3. Negative correlations between grey density and total number of ECT in CTRD patients controlling for age and sex.



Saggital Coronal Transverse

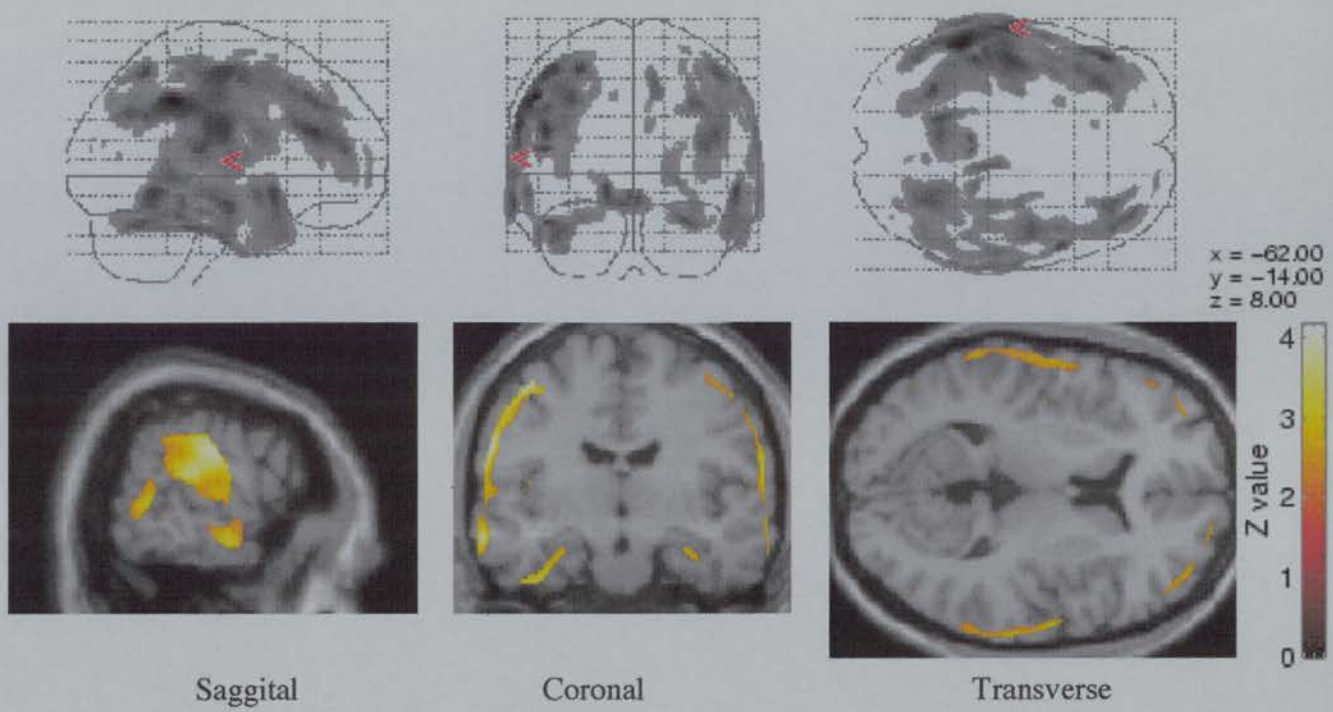
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
36, 46, 26 (5.75)	<0.001 (<0.001)	R. medial frontal (46/9)	8777	<0.001 (0.003)
-33, 48, 24 (4.70)	<0.001 (0.021)	L. medial frontal (9/ 10)		
-9, 60, 20 (4.68)	<0.001 (0.024)	L superior frontal (10)		
-18, -55, -12 (4.76)	<0.001 (0.017)	L. cerebellum	7122	<0.001 (0.006)
-23, -58, -8 (4.59)	<0.001 (0.034)	L fusiform (19)		
-17, -37, -2 (4.55)	<0.001 (0.04)	L lingual (19)		
8, 13, -4 (4.52)	<0.001 (0.046)	R caudate	1142	0.03 (0.103)
1, 7, -6 (4.41)	<0.001 (0.069)	R. caudate/ subgenual cing (25)		
-13, 14, 2 (3.38)	0.001 (0.90)	L caudate		
-53, 6, -16 (4.44)	<0.001 (0.06)	L. medial temporal (21)	1015	0.039 (0.129)
-41, 19, -32 (4.15)	<0.001 (0.181)	L superior temporal (38)		
-47, 15, -26 (3.95)	<0.001 (0.33)	L superior temporal (38)		
-60, -34, 34 (4.17)	<0.001 (0.16)	L. inferior parietal (40)	4423	<0.001 (0.026)
-62, -28, 26 (3.79)	<0.001 (0.49)	L. inferior parietal (40)		
-61, -48, 10 (3.63)	<0.001 (0.68)	L. superior temporal (22)		
57, -48, 40 (3.64)	<0.001 (0.67)	R inferior parietal (40)	3991	<0.001 (0.035)
54, -63, 16 (3.56)	<0.001 (0.75)	R medial temporal (39)		
65, -35, 14 (3.17)	0.001 (0.98)	R superior temporal (22)		

Figure 5.4. Negative correlations between grey density and number of psychiatric hospitalisations in CTRD.



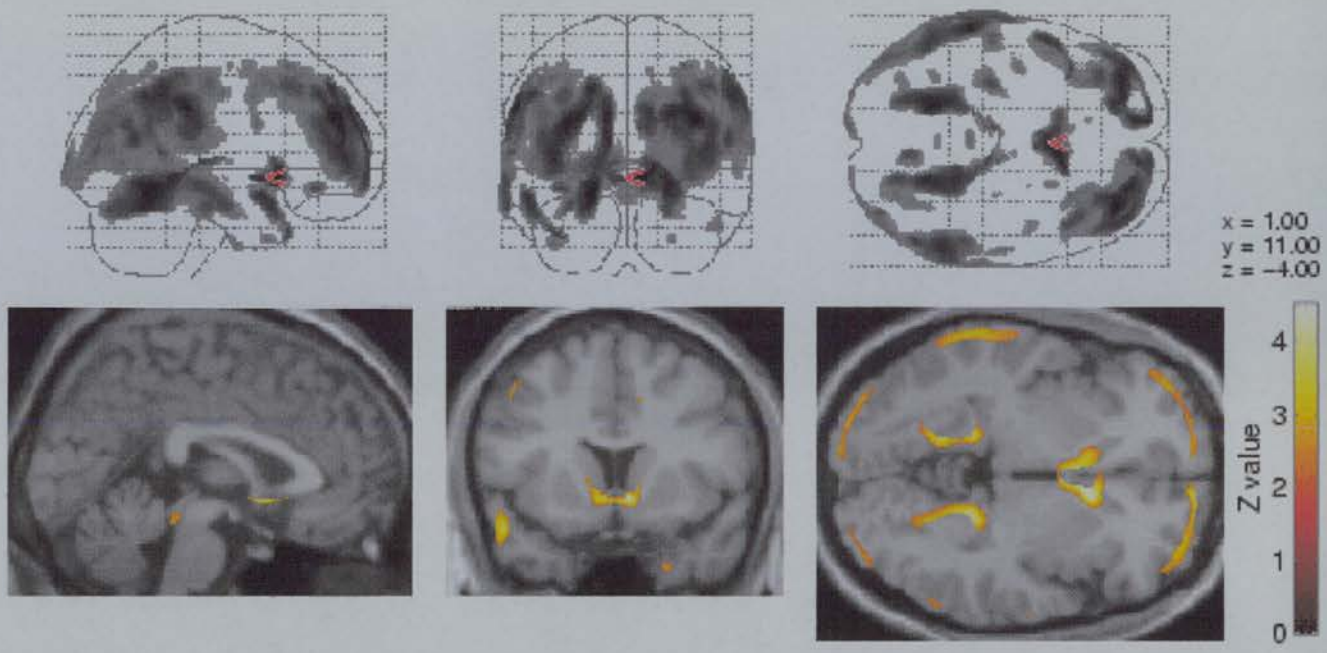
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-59, -35, 34 (4.87)	<0.001 (0.01)	L. inferior parietal (40)	7550	<0.001 (0.005)
-54, 5, -16 (4.28)	<0.001 (0.11)	L. medial temporal (21)		
-40, 21, -32 (3.87)	<0.001 (0.40)	L. superior temporal (38)		
37, 45, 26 (4.71)	<0.001 (0.021)	R. superior/ medial frontal (9)	5072	<0.001 (0.02)
27, 49, 32 (3.98)	<0.001 (0.30)	R. superior frontal (9)		
11, 58, 28 (3.77)	<0.001 (0.52)	R. superior frontal (9)		
-17, -53, -12 (4.70)	<0.001 (0.02)	L. cerebellum	3887	<0.001 (0.04)
-21, -58, -20 (4.38)	<0.001 (0.08)	L. cerebellum		
-19, -42, -6 (4.21)	<0.001 (0.14)	L. cerebellum		
-33, 48, 24 (4.57)	<0.001 (0.04)	L. superior frontal (10)	3089	0.001 (0.07)
-34, 51, 16 (4.05)	<0.001 (0.25)	L. medial frontal (46)		
-11, 55, 28 (4.04)	<0.001 (0.25)	L. superior frontal (9)		
6, 11 -4 (4.33)	<0.001 (0.09)	R. caudate	1004	0.041 (0.17)
3, 2 -4 (3.48)	<0.001 (0.83)	R. caudate		
-15, 14, 4 (2.77)	0.003 (1.0)	L. caudate		
23, -53, -16 (4.06)	<0.001 (0.24)	R cerebellum	4219	<0.001 (0.03)
22, -42, -6 (4.05)	<0.001 (0.25)	R cerebellum		
23, -58, -8 (3.94)	<0.001 (0.33)	R cerebellum		
55, -48, 40 (3.78)	<0.001 (0.51)	R Inferior parietal (40)	4594	<0.001 (0.02)
55, -62, 16 (3.61)	<0.001 (0.70)	R. medial temporal (39)		
54, -36, 52 (3.14)	<0.001 (0.99)	R. post central (40)		

Figure 5.5. Negative correlations between grey density and total duration of psychiatric hospitalisations in CTRD patients



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-53, -42, 42 (5.33)	<0.001 (0.001)	L. inferior parietal (40)	15234	<0.001 (<0.001)
-46, 34, 24 (4.34)	<0.001 (0.09)	L. medial frontal (9)		
-61, -16, 26 (4.24)	<0.001 (0.13)	L post central (2)		
-13, -54, -8 (4.05)	<0.001 (0.24)	L. cerebellum	5955	<0.001 (0.01)
-45, -34, -26 (3.91)	<0.001 (0.37)	L. cerebellum		
-1, -37, -12 (3.88)	<0.001 (0.40)	L. cerebellum		
54, 12, -10 (3.96)	<0.001 (0.32)	R superior temporal (38)	988	0.04 (0.41)
52, 17, -30 (3.19)	0.001 (0.98)	R. superior temporal (38)		
58, 8, -24 (3.04)	0.001 (0.99)	R. medial temporal (21)		
27, -58, -24 (3.77)	<0.001 (0.52)	R cerebellum	2646	0.002 (0.11)
25, -50, -22 (3.39)	<0.001 (0.90)	R cerebellum		
23, -36, -2 (3.23)	0.001 (0.97)	R cerebellum		
44, 40, 22 (3.69)	<0.001 (0.61)	R. medial frontal (10)	8486	<0.001 (0.003)
33, 38, 38 (3.69)	<0.001 (0.61)	R. medial frontal (8)		
38, 50, 14 (3.68)	0.003 (0.62)	R. medial frontal (46)		

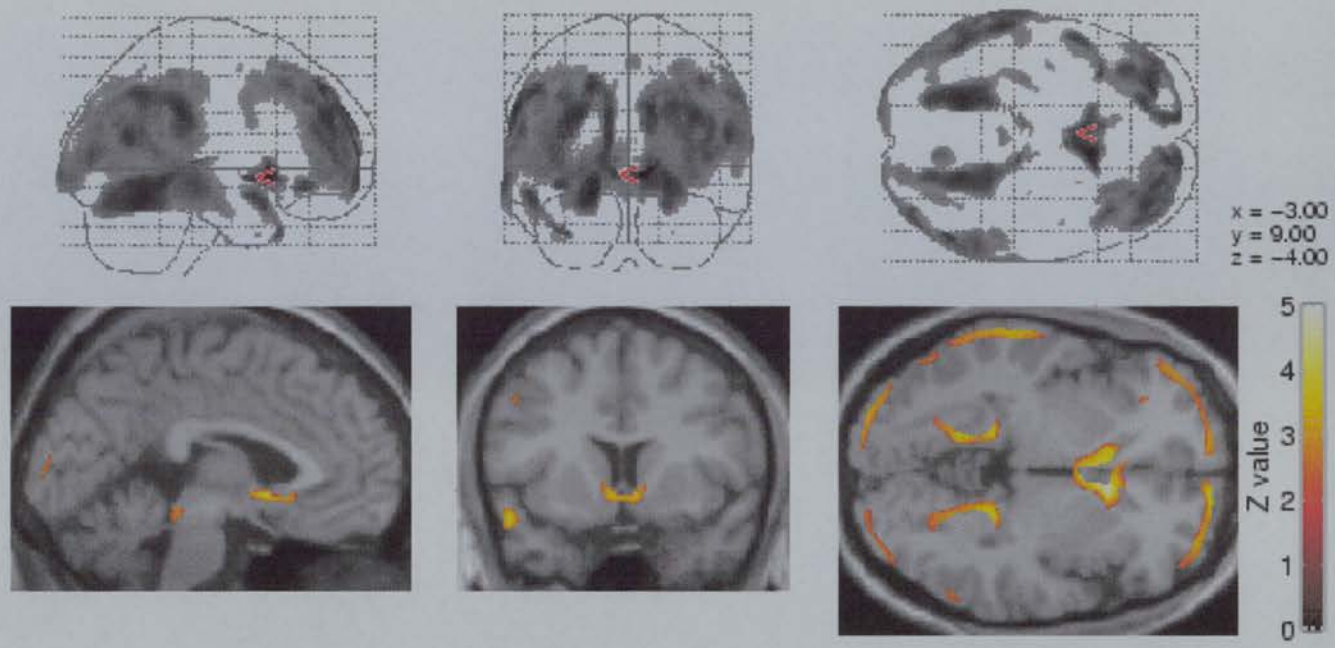
Figure 5.6. Negative correlations between grey density and total number of ECT in CTRD patients controlling for age and current severity of depressive symptoms (HRSD score).



Saggital Coronal Transverse

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
11, 15, -2 (4.66)	<0.001 (0.026)	R caudate	1216	0.026 (0.073)
1, 7, -6 (4.17)	<0.001 (0.17)	R caudate/ subgenual cing (25)		
-6, 11, -6 (3.60)	<0.001 (0.71)	L caudate		
37, 45, 26 (4.65)	<0.001 (0.027)	R. medial frontal (9)	5888	<0.001 (0.011)
24, 53, 32 (4.40)	<0.001 (0.074)	R superior frontal (9)		
31, 43, 34 (4.25)	<0.001 (0.13)	R. medial frontal (9)		
-60, -34, 34 (4.56)	<0.001 (0.040)	L. inferior parietal (40)	8444	<0.001 (0.003)
-53, -55, 40 (3.92)	<0.001 (0.36)	L. inferior parietal (40)		
-63, -33, 22 (3.73)	<0.001 (0.56)	L. superior temporal (22)		
-19, -56, -14 (4.54)	<0.001 (0.042)	L. cerebellum	7159	<0.001 (0.006)
23, -58, -8 (4.23)	<0.001 (0.14)	R fusiform (19)/ cerebellum		
22, -42, -6 (4.10)	<0.001 (0.21)	R fusiform (19)/ cerebellum		
-33, 48, 24 (4.54)	<0.001 (0.04)	L medial frontal (9/ 10)	4096	<0.001 (0.032)
-26, 49, 28 (4.35)	<0.001 (0.09)	L. superior frontal (9)		
-11, 61, 16 (4.34)	<0.001 (0.09)	L superior frontal (10)		
57, -50, 40 (4.03)	<0.001 (0.26)	R. inferior parietal (40)	5852	<0.001 (0.011)
54, -63, 16 (3.83)	<0.001 (0.45)	R medial temporal (39)		
54, -38, 52 (3.45)	<0.001 (0.86)	R. inferior parietal (40)		

Figure 5.7. Negative correlations between grey density and total number of ECT in CTRD patients controlling for age and type of depressive symptoms (Newcastle score).

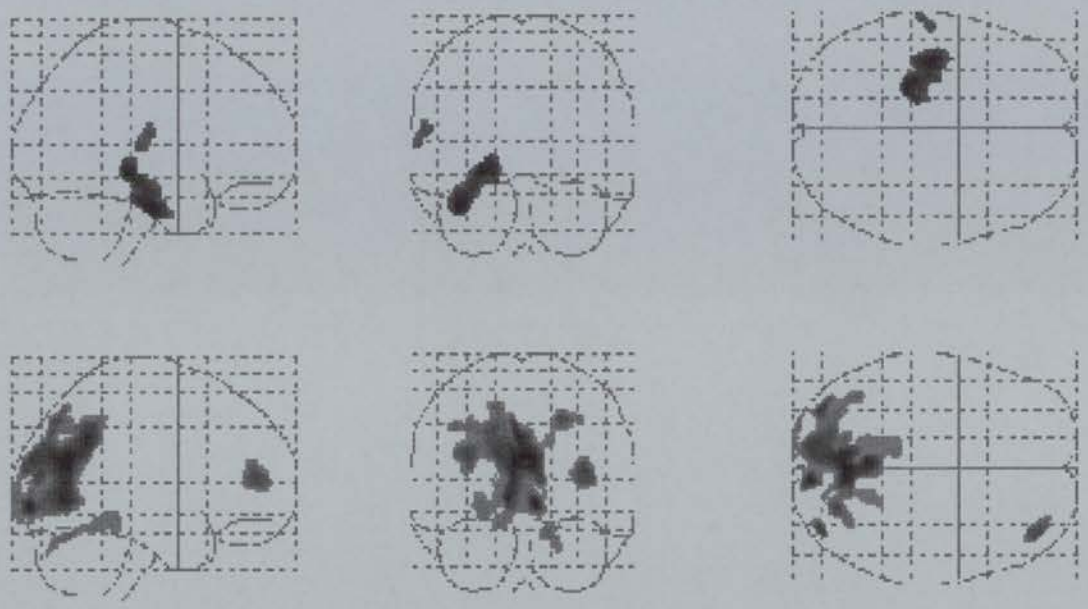


Saggital Coronal Transverse

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
11, 15, -2 (5.04)	<0.001 (0.005)	R caudate	1533	0.014 (0.028)
1, 7, -6 (4.16)	<0.001 (0.17)	R caudate/subgenual cing (25)		
-5, 12, -4 (3.99)	<0.001 (0.29)	L caudate		
-19, -56, -14 (4.65)	<0.001 (0.026)	L cerebellum	4512	<0.001 (0.025)
-22, -66, -18 (4.05)	<0.001 (0.25)	L cerebellum		
-18, -37, -2 (3.57)	<0.001 (0.75)	L. lingual (19)/ cerebellum		
-60, -34, 32 (4.36)	<0.001 (0.086)	L inferior parietal (40)	9179	<0.001 (0.003)
-52, -55, 42 (4.01)	<0.001 (0.27)	L inferior parietal (40)		
-66, -28, -8 (3.66)	<0.001 (0.65)	L medial temporal (21)		
-19, 44, 44 (4.32)	<0.001 (0.10)	L. superior frontal (8)	3846	<0.001 (0.039)
-33, 48, 24 (4.30)	<0.001 (0.10)	L medial frontal (9/ 10)		
-11, 61, 16 (4.30)	<0.001 (0.11)	L. superior frontal (10)		
37, 45, 26 (4.25)	<0.001 (0.13)	R medial frontal (9/ 10)	5879	<0.001 (0.011)
12, 56, 32 (4.18)	<0.001 (0.16)	R superior frontal (9)		
12, 62, -6 (4.04)	<0.001 (0.25)	R superior frontal (10)		
23, -59, -8 (4.24)	<0.001 (0.13)	R fusiform (19)	3750	<0.001 (0.042)
22, -52, -12 (4.06)	<0.001 (0.24)	R cerebellum		
22, -43, -6 (4.03)	<0.001 (0.26)	R fusiform (19)/ cerebellum		
55, -62, 18 (4.10)	<0.001 (0.21)	R medial temporal (39)	6450	<0.001 (0.009)
43, -83, 8 (3.58)	<0.001 (0.73)	R occipital (19)		
57, -48, 40 (3.45)	<0.001 (0.86)	R inferior parietal (40)		

Figure 5.8.Reductions and increases in grey matter density in CTRD compared to RD patients, controlling for age and total number of ECT previously administered

Reductions



Increases

Saggital Coronal Transverse

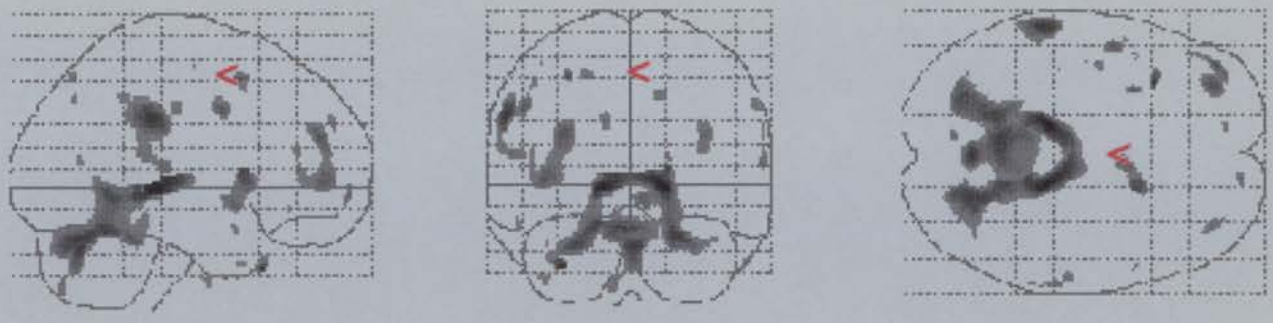
Reductions in grey density in CTRD patients

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-38, -16, -28 (3.63)	<0.001 (0.65)	L inferior temporal (20)	2213	0.005 (0.16)
-25, -29, -8 (3.52)	<0.001 (0.77)	L. hippocampus		
-30, -18, -18 (3.10)	0.001 (0.99)	L. hippocampus		

Increases in grey density in CTRD patients

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
1, -67, 24 (4.21)	<0.001 (0.14)	R. precuneus	13653	<0.001 (0.001)
7, -89, -4 (4.02)	<0.001 (0.25)	R. lingual (17)		
3, -53, 34 (3.97)	<0.001 (0.29)	L. precuneus		

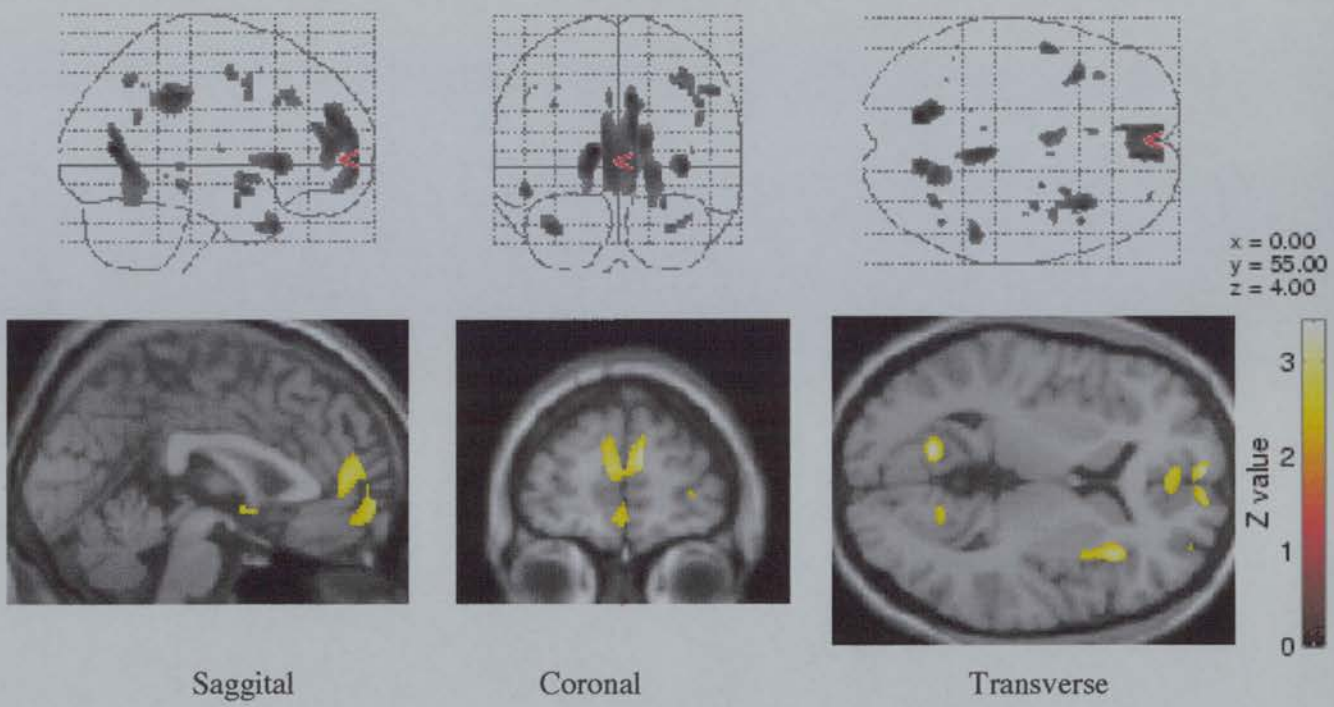
Figure 5.9. Negative correlations between grey matter density and total illness duration in CTRD patients, controlling for age and sex.



Saggital Coronal Transverse

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
16, -31, 0 (4.49)	<0.001 (0.05)	R parahippocampal (30)	7095	<0.001 (0.007)
-13, -31, 0 (4.44)	<0.001 (0.58)	L parahippocampal (30)		
-8, -24, 2 (3.71)	<0.001 (0.29)	L thalamus		

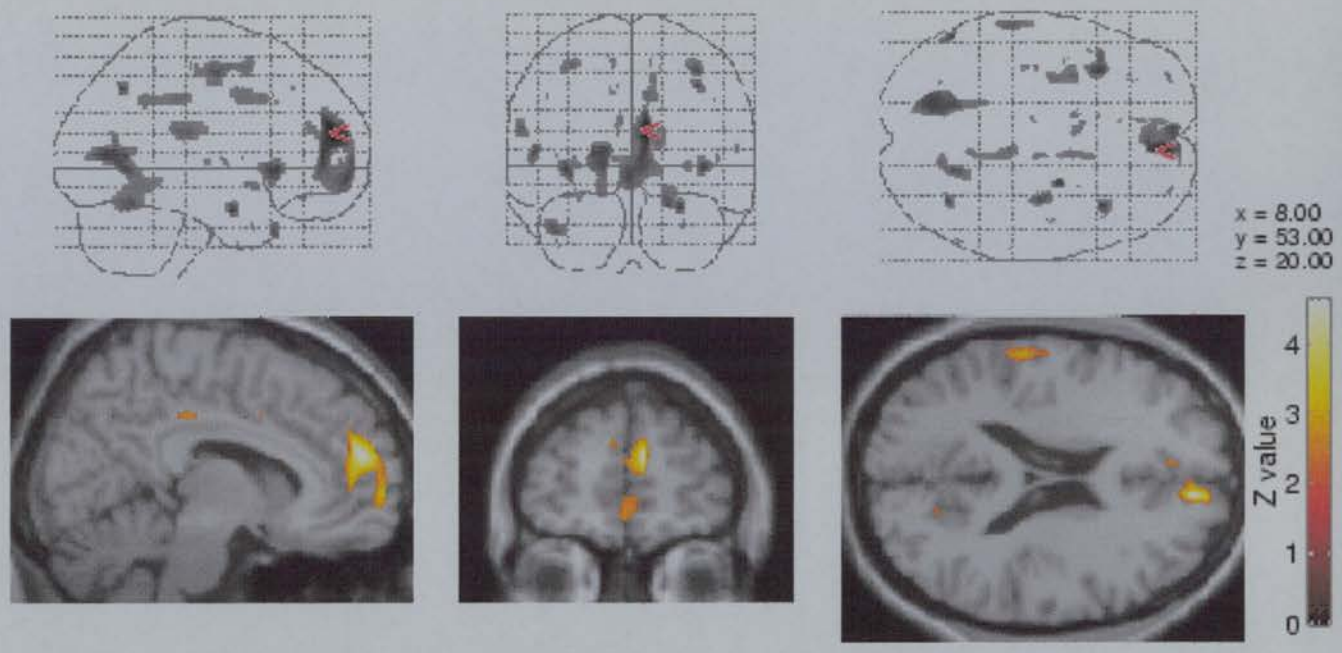
Figure 5.10. Negative correlations between grey matter density and current severity of depressive symptoms (HRSD score) in CTRD patients.



Saggital Coronal Transverse

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
8, 50, 26 (3.48)	<0.001 (0.83)	R. medial frontal (9)	3701	0.001 (0.045)
9, 58, 18 (3.39)	<0.001 (0.89)	R. medial frontal (10)		
-6, 49, 12 (3.26)	<0.001 (0.96)	L. medial frontal (10)		
15, -68, 14 (3.30)	<0.001 (0.94)	R cuneus	1261	0.025 (0.52)
19, -60, -4 (3.05)	0.001 (1)	R lingual (19)/ cerebellum		
19, -59, -20 (2.69)	0.004 (1)	R cerebellum		

Figure 5.11. Negative correlations between grey matter density and clinically rated motor retardation (Widlocher score) in CTRD patients, controlling for age.



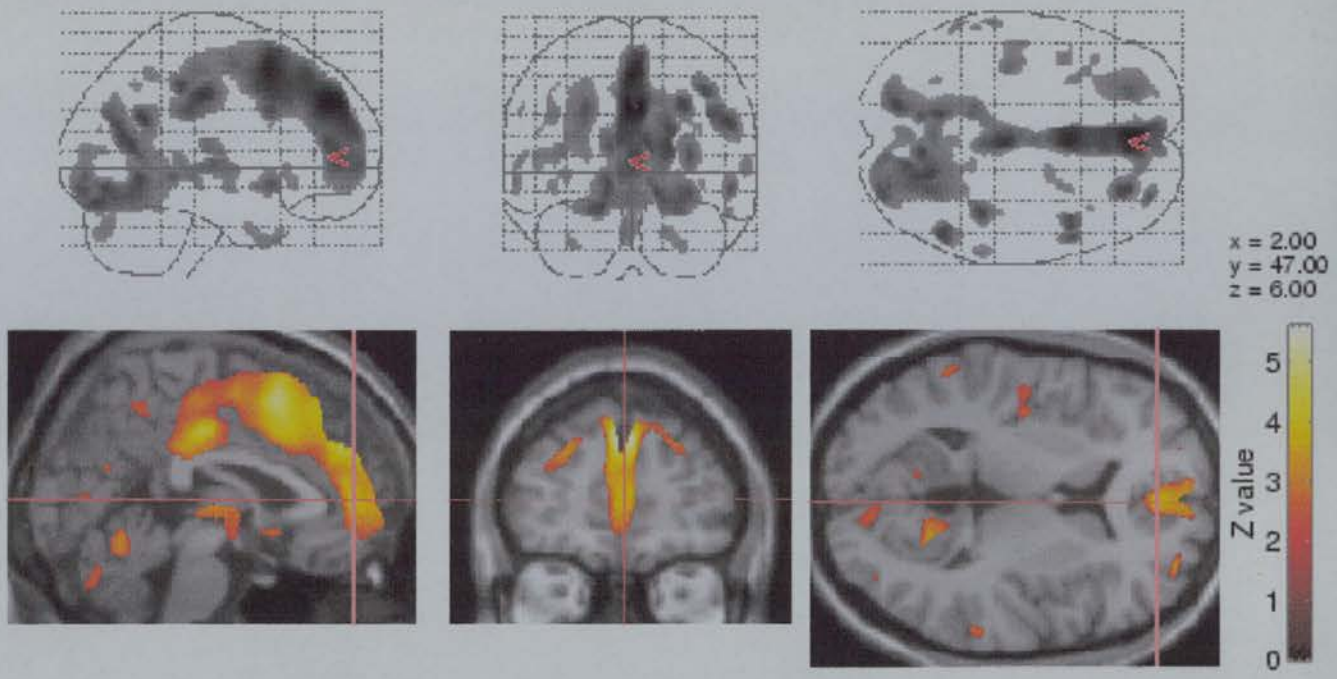
Saggital Coronal Transverse

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
8, 51, 20 (4.62)	<0.001 (0.03)	R. medial frontal (9/10)	2719	0.002 (0.08)
6, 47, 8 (3.61)	<0.001 (0.70)	R. medial frontal (9)		
-2, 60, -4 (3.35)	<0.001 (0.92)	L. medial frontal (10)		

Positive correlations between grey matter density and clinically rated motor retardation (Widlocher score) in CTRD patients, controlling for age.

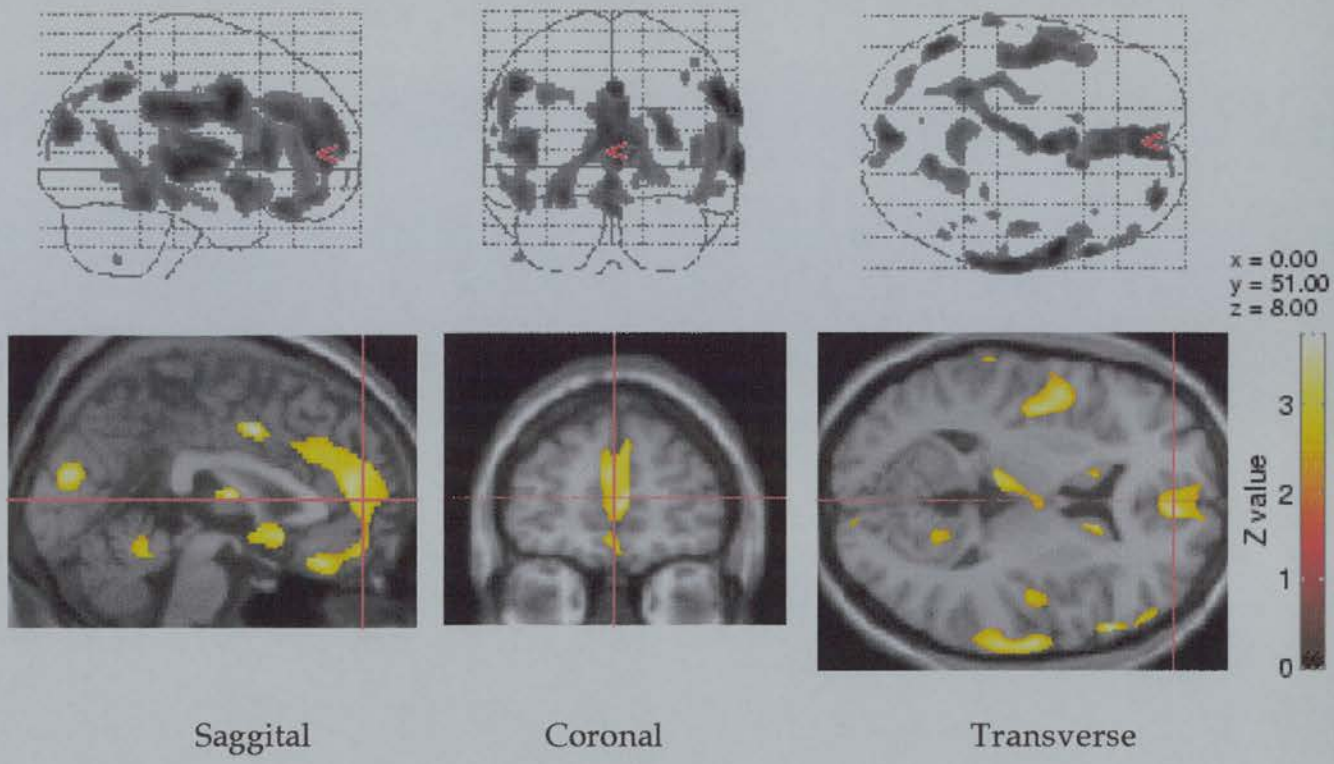
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
64, -37, -12 (4.83)	<0.001 (0.012)	R medial temporal (21)	2657	0.002 (0.047)
65, -21, -18 (4.10)	<0.001 (0.21)	R inferior temporal (20)		
62, -12, -24 (3.47)	<0.001 (0.84)	R medial temporal (21)		

Figure 5.12. Negative correlation between grey matter density and age in CTRD.



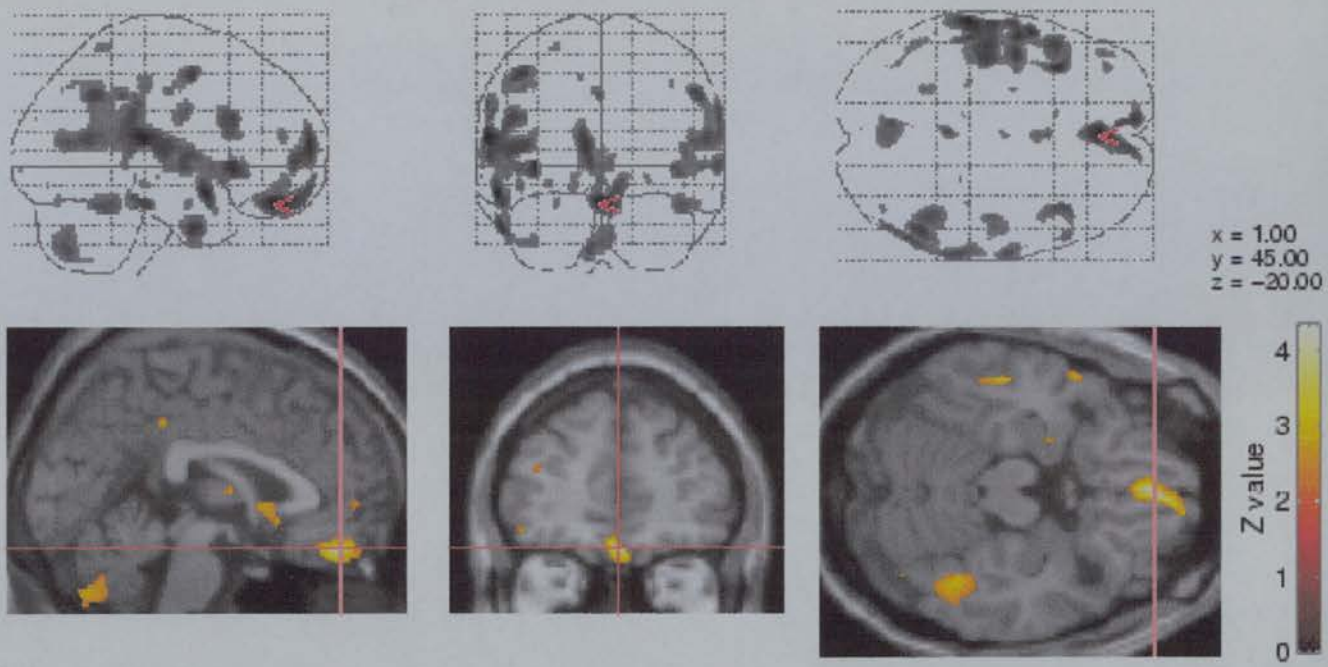
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-1, 48, 36 (5.61)	<0.001 (<0.0001)	L. fronto-medial (9)	20309	<0.001 (<0.001)
1, 12, 54 (5.13)	<0.001 (0.003)	R. superior frontal (6)		
3, -21, 40 (4.79)	<0.001 (0.015)	R Posterior cingulate (31)		
20,-63,14 (4.35)	<0.001 (09)	R posterior cingulate (31)	15637	<0.001 (<0.001)
-17, -81, -18 (4.22)	<0.001 (0.14)	L fusiform (19)		
14, -74, -10 (4.19)	<0.001 (0.15)	R lingual gyrus (17)		
-24, 43, 34 (3.82)	<0.001 (0.45)	L superior frontal (9)	1582	0.01 (0.36)
-32, 36, 34 (2.82)	0.002 (1)	L superior frontal (9)		
-24, 57, 10 (2.75)	0.003 (1)	L superior frontal (10)		

Figure 5.13. Negative correlation between grey matter density and age in RD.



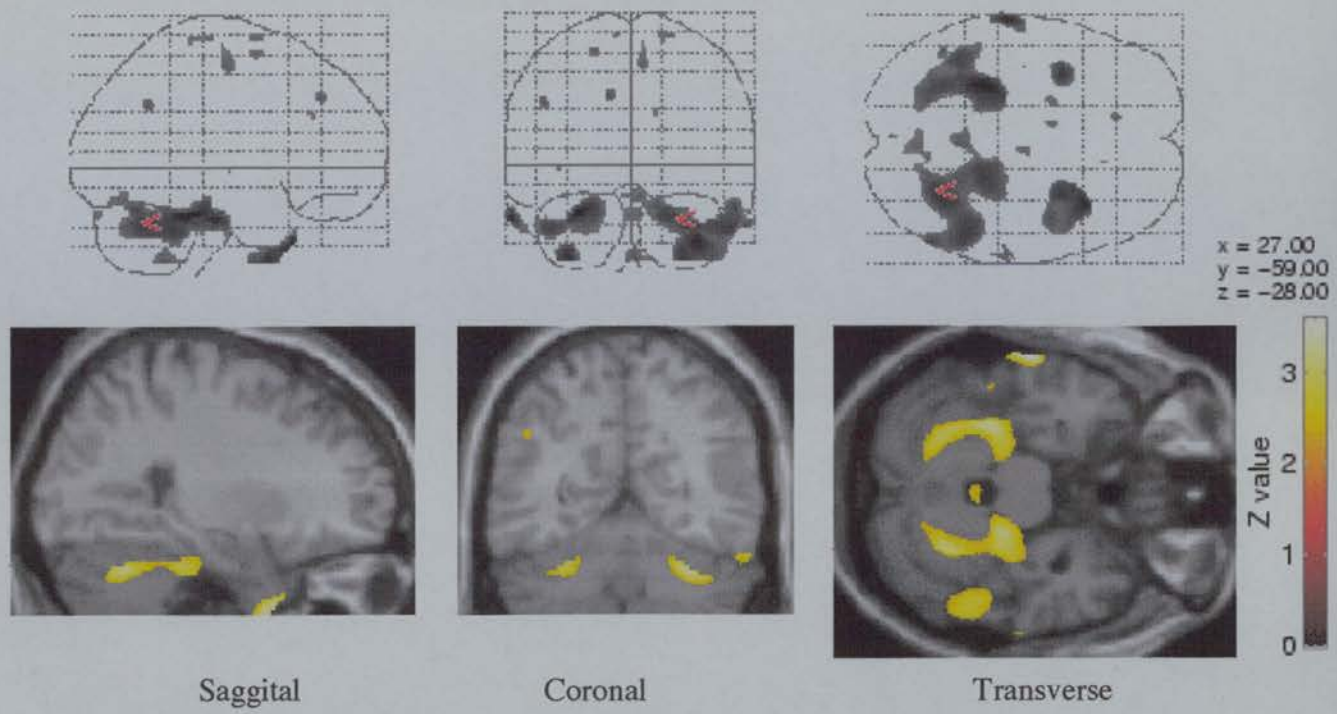
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
5, 47, 14 (3.91)	<0.001 (0.41)	R. fronto-medial (9/ 10)	7107	<0.001 (0.006)
5, 55, 4 (3.76)	<0.001 (0.59)	R. fronto-medial (10)		
-4, 46, 18 (3.63)	<0.001 (0.74)	L. fronto-medial (9)		
58, 4, 38 (4.63)	<0.001 (0.03)	R precentral gyrus (6)	5027	<0.001 (0.02)
65, -23, 32 (4.25)	<0.001 (0.15)	R. postcentral gyrus (2)		
68, -24, 2 (4.21)	<0.001 (0.17)	R sup. medial temporal (22)		
-48, -8, 12 (3.80)	<0.001 (0.53)	L. precentral (6)	3861	<0.001 (0.04)
-45, -22, 16 (3.38)	<0.001 (0.94)	L. postcentral gyrus (40)		
-49, 6, -14 (3.28)	0.001 (0.97)	L sup. medial temporal (38)		
-2, -12, 12 (3.74)	<0.001 (0.61)	L. thalamus	3323	0.001 (0.06)
-26, -44, -14 (3.67)	<0.001 (0.68)	L. fusiform		
-7, -20, 12 (3.53)	<0.001 (0.83)	L. thalamus		

Figure 5.14. Negative correlation between grey matter density and age of onset in RDs.



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-62, -28, 16 (4.43)	<0.001 (0.07)	L. superior temporal (42)	4583	<0.001 (0.023)
-56, 5, -14 (4.06)	<0.001 (0.27)	L medial temporal (21)		
-36, 20, 0 (3.96)	<0.001 (0.36)	L. insular cortex		
52, -54, 40 (3.56)	<0.001 (0.8)	R. Lateral parietal (40)	2094	0.004 (0.19)
57, -59, 14 (3.31)	<0.001 (0.96)	R. superior temporal (22)		
64, -33, 28 (3.24)	0.001 (0.98)	R. Lateral parietal (40)		
1, 45, -20 (4.33)	<0.001 (0.11)	R. fronto-orbital (11)	1265	0.021 (0.19)
5, 54, -18 (3.63)	<0.001 (0.73)	R. fronto-orbital (11)		
9, 61, -12 (3.19)	0.001 (0.99)	R. fronto-orbital (11)		
-8, 62, 12 (3.89)	<0.001 (0.43)	L. medial frontal (10)	928	0.043 (0.53)
-6, 54, 4 (3.37)	<0.001 (0.94)	L. medial frontal (10)		
5, 55, 2 (3.04)	0.001 (0.99)	L. medial frontal (10)		

Figure 5.15. Positive correlations between grey matter density and duration of tobacco smoking history in CTRD patients.



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-28, -33, -24 (4.10)	<0.001 (0.21)	L. cerebellum	3614	0.001 (0.047)
-29, -42, -26 (3.77)	<0.001 (0.51)	L. cerebellum		
-44, -49, -32 (3.21)	0.001 (0.97)	L. cerebellum		
37, 21, -40 (3.75)	<0.001 (0.54)	R. superior temporal (38)	1248	0.025 (0.52)
29, 6, -50 (3.41)	<0.001 (0.88)	R. superior temporal (38)		
31, 16, -44 (3.23)	0.001 (0.97)	R. superior temporal (38)		
30, -58, -30 (3.42)	<0.001 (0.87)	R. cerebellum	5047	<0.001 (0.018)
20, -36, -26 (3.30)	<0.001 (0.94)	R. cerebellum		
52, -45, -32 (3.29)	<0.001 (0.95)	R. cerebellum		

Negative correlations between grey matter density and duration of tobacco smoking history.

Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
38, -82, -14 (4.36)	<0.001 (0.08)	R cerebellum	3484	0.001 (0.052)
30, -84, -18 (3.60)	<0.001 (0.71)	R cerebellum		
37, -75, -18 (3.53)	<0.001 (0.78)	R cerebellum		

ECT received were closely correlated in the CTRD group, it is not surprising that correlations between grey matter density and these three variables were almost identical. As figures 5.2, 5.3 and 5.4 show, cumulative ECT and total number of hospitalisations were negatively correlated with bilateral superior frontal and inferior parietal gyri, bilateral medial and superior temporal gyri and bilateral caudate. There were similar negative correlations between extensive areas of bilateral temporal grey matter density and cumulative hospital admissions, involving frontal regions to a lesser degree (figure 5.5). Notably, all three variables did not correlate with either hippocampal or rostral anterior cingulate grey matter. The correlations with lifetime numbers of ECT were unaffected after accounting for the current severity of depression (using the HRSD score as a co-variate, figure 5.6) or the degree of endogenicity (using the Newcastle scale score as co-variate, figure 5.7). Hence, increasing cumulative severity, and not current severity or type of the illness, was associated with neocortical reductions in grey matter density.

The group comparison of grey matter density between the CTRD and RD groups was repeated, controlling for the number of ECT administered as well as age. As expected, (figure 5.8) the only significant reduction was in left hippocampal grey

matter density, the neocortical reductions in the CTRD no longer present. Thus, reduced left hippocampal grey matter density in the CTRD group was unrelated to the cumulative illness severity (or lifetime number of ECT). Interestingly, the large increases in precuneal grey matter and the small increases in bilateral cerebellar grey also remained, suggesting that these too were unrelated to the cumulative severity of depression.

There were no significant correlations between grey matter density and number of ECT in the recovered group.

B. Estimated cumulative illness duration

In contrast, the estimated total duration of illness did not correlate with neocortical grey density reductions but instead with brain stem/ posterior cingulate grey matter reduction (figure 5.9).

C. Clinical features of depressive illness

Both the severity of current depressive symptoms, measured with the HRSD (figure 5.10), and clinically rated psychomotor retardation, measured by the Widlocher scale (figure 5.11), were significantly negatively correlated with bilateral medial frontal gyrus (Brodmann areas 9 and 10). This is not surprising as both clinical measures were highly inter-

correlated. In contrast, there were no significant correlations between grey density and Newcastle scale score.

Finally, the nine patients with CTRD who had at some time in their illness experienced hallucinations or delusions were compared with the eleven who had not. Patients who had had psychotic symptoms showed small grey density reductions in right inferior and right superior frontal cortex, before correction for multiple correction.

D. Current age and age of onset.

There was no correlation between age and grey matter density in the controls. Both patient groups, however, showed highly significant negative correlations between grey matter density and age (figures 5.12 and 5.13) in bilateral fronto-medial prefrontal cortex (Brodmann areas 9 and 10), extending around the medial surface, including the cingulate and extending posterior to the precentral gyrus. Brodmann areas 9 and 10 grey matter also negatively correlated with age of onset in the RD patients (figure 5. 14), but not the CTRD group. There were no other significant correlations with age of onset. Age was also positively correlated with cerebellar grey matter, particularly in the RD group.

E. Duration of smoking history

Surprisingly, there was a strong positive correlation between the number of years a patient had smoked tobacco and bilateral cerebellar grey matter, in the same regions in which there were group differences in grey matter density (figure 5.15). The correlation was significant even after correction for multiple comparisons.

5.4 Discussion

5.4.1 General points on the group comparisons of MRIs

There are two broad points:

1. CTRD patients have MRIs which differ from two comparator groups.

At its simplest, the results show that only CTRD patients had differences in tissue density in comparison to healthy controls and recovered patients. The pattern of differences in the CTRD group compared with controls was almost identical to the comparison with recovered patients. This is particularly important when considering unpredicted differences in tissue compartments- the argument for these being chance findings is weakened, if found in two groups.

There was no difference between the recovered and control groups in any tissue compartment and therefore they could be formed into a single group. This had the effect of increasing the power of the group comparison with the CTRD group. It is interesting that the recovered patients had no tissue differences compared to healthy controls. This contrasts with the recent finding of hippocampal volume reductions in recovered elderly women (Sheline *et al*, 1996).

2. SPM analysis may be more sensitive and comprehensive than conventional volumetric analysis.

Conventional volumetry simplifies the analysis of MRI data into counting numbers of voxels, and therefore volume, in only specific regions of interest formed by a priori hypotheses. In contrast, VBA examines the intensity of all voxels and is hypothesis free. The core assumption in traditional volumetry is that the MRI reflects structure. However, this is a simplified interpretation of MRI data- T1 weighted MRI images are a "snapshot" of cerebral water distribution at a point in time. The intensity of a single picture element, representing the net signal from a block of tissue (a voxel) depends on the water content of the voxel. In turn, the voxel water content depends on the tissue characteristics (eg lipid content) but may also depend on focal biochemistry and blood flow, which may be a temporary, state dependant change. Thus, T1-weighted MRIs may reflect both anatomical and state dependant effects.

Clearly, voxel intensity differences are important as these distinguish the CTRD group- in fact, reductions of T1 intensity values in depression has been previously found. However, as will be illustrated later, the form of VBA used, SPM, may detect a range of changes from gross structural atrophy, lesser degrees of structural change with changes in tissue density

only, to differences possibly representing local change in the biochemical environment. This is made possible by examining complimentary changes in all three tissue compartments.

5.4.2 An interpretation of MRI changes in patients with CTRD

The results of SPM analysis suggest two areas of atrophy in the CTRD group- right basal ganglia and bilateral, particularly right, frontal lobes. This prediction was confirmed on conventional volumetric analysis. In the SPM analysis, there was both reduced right striatal tissue density and an increase in overlying CSF. In the frontal lobes, there were large reductions in prefrontal white matter, particularly on the right, with a corresponding increase in bilateral CSF. However, grey matter was spared in left prefrontal cortex, with both increases and decreases in right grey matter. One possiblilty is that the CTRD group mainly had white matter atrophy, with relative grey matter preservation: with shrinkage of the right frontal lobe, grey matter moved away from the skull, producing apparent decreases in grey matter on the cortical surface, but increases at the edge with white matter.

Other volumetric studies support these findings- the most reliably demonstrated structural difference found during depression

is of frontal lobe and basal ganglia volume reductions (Soares & Mann, 1997). Whether this represents state dependant change or is irreversible cannot ultimately be answered by this cross-sectional study, especially as apparent atrophy on MRI has been found to reverse to some extent with illness resolution in conditions such as anorexia nervosa and alcohol dependence (Swayze *et al*, 1996) (Trabert *et al*, 1995). However, as will be discussed below, the results suggest that neocortical change may be related to the cumulative severity of illness, and thus, acquired.

In contrast, focal changes in tissue water or biochemical composition without volumetric change, may explain the reciprocal decreases and increases in grey and white matter densities respectively in Brodmann area 24). A consideration of MRI signals and of the method of analysis may be useful at this point. With atrophy, CSF replaces grey and white matter and produces a darkening of the voxels. If, however, water density or content diminishes without cell death, possibly through focal biochemical change or sclerosis, the T1 signal would appear brighter, with signal intensities resembling white matter. As voxels are segmented by the approximate spatial distributions of tissue and by voxel intensity, and as hippocampal grey and white matter is closely intertwined,

brighter voxels may be segmented into the white matter compartment instead of grey, reducing grey matter density, but increased white matter densities. Because of this, and as there was no increase in CSF in the lateral ventricle abutting on to the hippocampus, no volumetric change would be expected on the basis of these results. This contrasts with the results from Sheline et al. (Sheline *et al*, 1996) who found reduced bilateral hippocampal volume, particularly left sided, in recovered elderly women with a history of recurrent depression, in a high resolution volumetric MRI study. Hippocampal volume reduction was correlated with total illness duration.

Similarly, biochemical and not volumetric change may explain the changes in Brodmann area 24 (rostral anterior cingulate cortex). This area is of particular interest as recent evidence suggests that hypoperfusion in this area may predict treatment non-response (Mayberg, 1997; Mayberg *et al*, 1997). The results are consistent with this hypothesis, but do not support Drevet's hypothesis of volumetric change in Brodmann area 25 (subcallosal anterior cingulate) as a marker for familial affective disorder (Drevets *et al*, 1997). However, both patient groups in this study were a mixture of both familial and non-familial affective disorders, and so this hypothesis could not be directly examined.

Interestingly, change in both these areas was not related to the cumulative severity or total duration of illness.

The large grey matter density reductions in the left temporal lobe were not accompanied by reductions in white matter density or an increase in CSF. Presumably this reflects subtle structural change or a change in the biochemical environment. There is a large body of evidence suggesting reduced temporo-limbic perfusion or metabolism during depression (Amsterdam & Mozley, 1992; Austin *et al*, 1992b; Mayberg *et al*, 1994), but equivocal evidence for atrophy - in elderly patients, chronicity may be associated with increased ventricle to brain ratio (Roy-Byrne *et al*, 1988), with decreased right temporal volume (Altshuler, 1993) and with decreased amygdala-hippocampus volume (Axelson *et al*, 1993). The results of this study, however, would predict no volumetric change, as was confirmed on volumetric analysis.

There was increased white matter density in the anterior corpus callosum in the CTRD group. There has been reports of increases, decreases and no difference in callosal cross-sectional area in the literature (Hauser *et al*, 1989; Coffman *et al*, 1990; Wu *et al*, 1993), but their significance is unknown. Interestingly, Wu et al (Wu *et al*, 1993) found increased callosal size in unipolar patients. There was also evidence of

increased cerebellar grey density in only the CTRD group. There is some evidence that cerebellar structures may form part of the network involved in emotional regulation, and that metabolic differences exist in cerebellar vermis in those with depression (Bench *et al*, 1992; Shah *et al*, 1992). The increases in grey and white matter densities in the precuneal region are more difficult to understand with current models of depression.

5.4.3 An interpretation of the clinical correlates of MRI changes

By allowing correlational analysis, SPM may help identify some of the influences in producing brain changes in CTRD. There were three important clinical correlates of grey matter density (cumulative severity of depression, psychomotor retardation and age) and one unexpected correlate (tobacco smoking).

A. Cumulative severity

Cumulative severity of illness (lifetime number of ECT) not purely illness duration, was associated with neocortical frontal and temporal grey matter density reductions in in the CTRD group, suggesting that these changes were acquired. The hippocampal and rostral anterior cingulate reductions were not related to cumulative severity, which was confirmed when the CTRD and RD groups were

compared controlling for the number of ECT given- grey matter density reductions in the left hippocampus were still found in the CTRD group.

Although there are no studies directly comparable to this, there is some evidence suggesting that chronicity, independent of diagnosis, may be associated with temporal lobe changes in a number of ways.

First, Ebmeier et al (Ebmeier *et al*, 1998) have shown that late onset depression is associated with reduced temporal lobe perfusion which is related to the severity of periventricular hyperintensities. Such hyperintensities are associated with a poorer prognosis and treatment resistance (Hickie *et al*, 1995). Greenwald et al (Greenwald *et al*, 1996) have also demonstrated that patients with late-onset depression have left medial temporal lobe atrophy. Thus it may be that disrupting the function of the left temporal lobe acts as a vulnerability factor in maintaining illness.

Second, it is well established that patients with depression show a dysregulation of the hypothalamic-pituitary-adrenal axis. Up to 70% of patients have raised levels of cortisol, which generally are not suppressed by dexamethasone (Dinan, 1994). A continuing positive dexamethasone suppression test, despite apparent clinical improvement, may predict rapid relapse and possibly chronicity

(Amsterdam *et al*, 1983; Targum, 1983). Animal work suggests that chronically raised cortisol can facilitate hippocampal neuronal death, which in turn may cause dysregulation of the HPA-axis (Sapolsky *et al*, 1986; Jacobson & Sapolsky, 1991). Importantly, dysregulation of the HPA axis is not diagnosis specific, and can also be found in patients with schizophrenia, who have reduced hippocampal volumes. Chronicity in schizophrenia also appears to associate with reductions in left temporal lobe volumes (DeLisi *et al*, 1991). However, since hippocampal damage may disinhibit the HPA axis and cause hypercortisolaemia, these associations do not establish the direction of the effect. Interestingly, our chronic patients did not exhibit dexamethasone non-suppression, suggesting that hypercortisolaemia may not be an important factor maintaining chronicity in this sample. However, since we did not obtain baseline measures of cortisol and this was a cross-sectional study, the possibility of present or previous HPA dysfunction cannot be discounted.

Third, grey matter change may be an antecedent to chronic depressive symptoms or their treatment. Obstetric complications may be more frequent in patients with early onset depression or with bipolar disorder (Done *et al*, 1991; Guth *et al*, 1993; Kinney *et al*, 1993). In schizophrenia, such

complications have been linked to neurodevelopmental brain abnormalities, in particular left temporal lobe volume reduction (Waddington, 1993; O'Callaghan *et al*, 1995), which may reflect reduced cerebral lateralisation. One study (DeLisi *et al*, 1991) found that patients with chronic schizophrenia had smaller left temporal lobe volumes than a reference group of patients examined during their first illness episode. Similarly, our patients with chronic depression showed a tendency to less lateralisation, if compared with recovered patients or healthy controls. It is, therefore, possible that neurodevelopmental abnormalities in patients with unipolar depression, particularly affecting the left temporal lobe, may predispose to chronicity.

B. Age and psychomotor retardation

In both patient groups, older patients had later onset illness and had fewer episodes of depression than younger patients. In only the patient groups was older age associated with reduced grey matter density in large areas in medial frontal cortex, particularly Brodmann areas 9 and 10, as well as parts of the cingulate cortex. This could not be attributable to general ageing- controls did not exhibit such a correlation.

In the CTRD group, patients with later onset depression had more melancholic features, measured by the Newcastle scale, motor retardation being a feature of melancholia. Both older age and increasing motor retardation correlated with reduced medial prefrontal grey matter density, particularly Broadman areas 9 and 10. Recovered patients had residual psychomotor retardation, previously also had melancholic depression and exhibited grey matter correlations with age in the same way as CTRD patients. The RD patients also showed a negative correlation between age of onset and medial prefrontal grey matter density. Thus, these results suggest that the later the onset of depression, the larger the reduction in grey matter density in medial prefrontal regions, regardless of outcome, and that this reduction was a marker for increasing motor retardation found only in those had depression. Further, as cumulative severity, or number of ECT was related to the severity of retardation in the CTRD patients, illness severity and age of onset may interact- thus, patients with severe late onset depression may be expected to have the greatest reduction in medial prefrontal grey density. This conclusion has support from existing literature. Functional imaging studies suggest that prefrontal hypoperfusion may be associated with motor slowing. Curran et al (Curran *et al*, 1993) for example, found

an age effect in medial prefrontal perfusion in depressed patients- older patients with melancholic depression showed greater medial prefrontal hypoperfusion than younger patients. Structural change during depression is most commonly found in the elderly, particularly in those with severe illness and particularly in frontal regions (Coffey *et al*, 1993). Further, on recovery, residual motor slowing has been found in both young (O'Brien *et al*, 1993) and elderly (Abas *et al*, 1990) patients, although associated structural change is found only in the elderly (Abas *et al*, 1990). Thus, although it is acknowledged that late onset depression in the elderly is associated with structural change (Krishnan *et al*, 1997), the results presented here suggest that older age and age of onset in non-elderly populations is also associated with structural change. Taken with the findings of fronto-striatal atrophy, a possible interpretation is that motor retardation in melancholic depression is not fully reversible, even on recovery, which suggests an enduring, accumulative effect of depression associated with biological change in fronto-striatal regions, and which becomes more prominent with increasing age.

There are a number of interpretations of the association between age and medial frontal grey matter reductions in the depressed group. As age more than age of onset had greater

correlation, it may be that depression, regardless of outcome has a "premature ageing" effect in these areas. It may also be that depression has an exaggerated effect in the presumably more vulnerable, older brain. It is known, for example, that medial frontal areas, particularly cingulate, show age-related metabolic reductions in normal controls (Martin *et al*, 1991). Although it is possible that the controls in this study had age related changes, any such changes were not of sufficient magnitude to produce focal changes in T1 values. It may be that such an effect reflects a neurotoxic effect of, for example, cortisol. However, both recovered and chronically depressed patients were dexamethasone suppressors, suggesting no ongoing hypercortisolaemia. Further, the hippocampus and not the cingulate, is usually regarded as the structure most susceptible to cortisol induced damage (Sapolsky *et al*, 1986). Alternatively, it may be that the balance of aetiologies for depression changes with age, as is the case in old age depression. The results of this study support the notion that the increasing risk of severe depression with age (Eagles & Whalley, 1985) may be mediated by structural brain changes, suggesting that structural change in fronto-medial cortex is a marker or vulnerability factor for depression in older age, but not predictive of outcome. However, as this

study was cross sectional, the causal relationship cannot ultimately be resolved, requiring longitudinal studies.

The existing literature provides support for the involvement of a striato-frontal system (Robbins *et al*, 1992) and, in particular, inferior and medial frontal dysfunction in the biology of depression and an association with psychomotor retardation (Austin *et al*, 1992b; Curran *et al*, 1993; Mayberg *et al*, 1994) (Bench *et al*, 1992; Dolan *et al*, 1994). In fact, some authors regard motor retardation as a core feature of depression, particularly in patients who exhibit melancholic symptoms(Widlöcher, 1983; Parker *et al*, 1993). This concept has recently undergone a renaissance, strengthened by the findings from neuroimaging and neuropsychological studies. Functional imaging studies, for example, have found reductions in blood flow in frontal areas, related to increasing psychomotor retardation (Bench *et al*, 1993) (Dolan *et al*, 1993) (Curran *et al*, 1993). Medial orbito-frontal cortex activation has also been found in association with reinforcement and reward (Rolls *et al*, 1997) and with induction of different mood states in healthy volunteers (Pardo *et al*, 1993; George *et al*, 1995; Baker *et al*, 1997). Further, recent studies have found in vivo changes in right striatal dopamine suggestive of reduced dopamine release in depression, related to the severity of motor retardation

(Ebert *et al*, 1994a; Ebert *et al*, 1996; Shah *et al*, 1998), again implicating fronto-striatal pathways in depression. Characterisation of cognitive deficits in depression also lend support to a fronto-striatal deficit, which may be irreversible, raising the possibility of a "fronto-striatal or fronto-subcortical" dementia (reviewed in Robbins *et al*, 1992). Massman et al (Massman *et al*, 1992), for example found that a subgroup of depressed patients exhibited a "subcortical dementia" memory profile, a prominent feature being difficulty with speed related tasks. Further, motor speed, unlike most other cognitive measures, may not normalise with recovery from depression (Abas *et al*, 1990) (Beats, 1996) (O'Brien *et al*, 1993), is not sensitive to diurnal variation during depression, unlike most other psychometric measures (Moffoot *et al*, 1994), and correlates negatively with the number of depressive episodes and with measures of cerebral atrophy (Abas *et al*, 1990), suggestive of an irreversible, cumulative effect.

As with hypercortisolism, temporal lobe changes and chronicity, these psychomotor and structural changes may not be diagnosis specific. There are, for example, parallels with findings from schizophrenia where frontal lobe atrophy and hypoperfusion has been associated with the negative

symptoms of schizophrenia(Dolan *et al*, 1993) which are also regarded as an expression of a reduced dopaminergic function in the mesolimbic system. In another study (Chua *et al*, 1997), the severity of left ventromedial prefrontal atrophy correlated with the degree of psychomotor poverty (ie poverty of speech, flattening of affect, retardation of action) in schizophrenia. In fact, chronically depressed patients have been found to have similar levels of negative symptoms compared to patients with schizophrenia (Harvey *et al*, 1997). Such converging evidence raises the issue of the difficulty in separating "negative symptoms" from some of the symptoms of depression and may argue not only for a phenotypic similarity between slowing in depression and negative symptoms in schizophrenia, but a shared, final common biological pathway, speculatively involving dopamine in medial frontal regions.

C. Tobacco smoking

Unexpectedly, there was a strong positive correlation between the duration the CTRD patients had smoked and grey matter density in bilateral cerebellum. The CTRD patients had a tendancy to have been smoking for longer than the other two groups, and the cerebellar increases were unrelated to

any of the clinical factors. Tobacco contains a number of psychoactive substances, including nicotine which can have effects on cholinergic receptors. It has been claimed, for example that people who smoke tobacco have an altered risk of dementia risk of dementia (Leibovici *et al*, 1999; Merchant *et al*, 1999; Wang *et al*, 1999). Thus, it may not be unexpected to find cerebral metabolic change in association with smoking. Despite this, the association with cerebellar grey matter density remains unexplained.

Three other regions had grey matter changes unrelated to any of the clinical factors examined- the hippocampi, the rostral anterior cingulate and the precuneus. The rostral anterior cingulate (Brodmann area 24) reductions only appeared in the CTRD group, suggesting that it could be a state-independant marker of treatment non-response, as suggested by Mayberg (Mayberg *et al*, 1997). Interestingly, in the patients who had recovered, there was a trend positive correlation between number of ECT and rostral anterior cingulate grey matter density. Hippocampal change in T1 values were also unrelated to any clinical facotrs and were found only in the CTRD group, suggesting that these changes may be state independent and a marker of treatment resistance and chronicity. The correlates of the

hippocampal changes will be examined in the next chapter. Ultimately, however, the large changes in precuneus remain unexplained.

5.4.4 Defining chronicity and treatment resistance

The patient sample was chosen to be extreme examples of chronicity and on a continuum of treatment responsiveness (Bonne *et al*, 1996), and to maximise the likelihood of having a sample which exhibited cerebral abnormalities. Two years of continuous symptoms was chosen to define chronicity as the rate of recovery more or less reaches a plateau after about eighteen months of illness (Keller *et al*, 1982; Keller *et al*, 1984), suggesting the remaining patients form a stable, unchanging cohort of patients. In fact, the sample of CTRD patients examined well exceeded two years of active illness, having a mean episode duration of 197 weeks (almost 4 years of continuous illness).

The definition of treatment resistance is necessarily arbitrary, and varies considerably in the literature, most noticeably with country. The criteria that were used in this study for judging the adequacy of antidepressant dose and duration was based on British National Formulary recommended maximum doses, ensuring that the sample would be considered as being treatment resistant by most British

psychiatrists. In fact, the sample far exceed the minimum criteria of treatment resistance, having had trials of multiple adequately dosed antidepressants for sufficient periods of time (Appendix 5.1).

Patients may be divided into having relative and absolute treatment resistance depending on whether an adequate dose and duration of antidepressant had been prescribed. However, it could be argued that inadequate treatment itself may predispose to cerebral change, if persistent hypercortisolism mediates the neuronal damage. This is further supported with the finding that chronicity is predicted by longer duration of illness prior to treatment (Scott, 1988), suggesting a progressive damaging effect of untreated illness. Such a model may not be fully adequate to explain how treatment resistant patients can still effect full recoveries.

5.4.5 Measuring cumulative illness severity, total illness duration and duration of illness before adequate treatment.

Accurately measuring time related illness features requires a longitudinal study. This study has the disadvantage of being cross-sectional. Thus, measurements of lifetime illness duration, severity over time and duration of illness

without treatment may have varying reliability, dependent on the quality of retrospective information from casenotes. Fortunately, full clinical documentation was available on both patient sample groups.

The advantage of using number of ECT treatments, total number of hospital admissions and total duration of in-patient stay as indices of cumulative illness severity is that these data could be accurately measured. As hospital admission and ECT are usually reserved for patients who are severely disabled with illness, or for those with intractable illnesses requiring assessment and treatment, it is not unreasonable to use these indices as measures of illness severity over time. In contrast, the estimate of lifetime illness duration has to be regarded with caution as it is more dependant on patients' recollections and the quality of clinical documentation. An acceptably accurate estimate of duration of illness prior to adequate treatment could not be obtained, as it was greatly dependant on patients' recollections of distant events, which itself could be subject to distortion by their present mental state. Such an estimate requires accurate assessment and documentation at first presentation and ideally, corroboration by third parties at the time. As these were not reliably available, an estimate of illness before treatment had to be abandoned.

5.4.6 Alternative interpretations of the data

Although the groups were very closely matched, it could be argued that the changes were related to treatment, specifically to ECT. Whether such as association is causal, and if so in which direction is not clear. However, there is little evidence that ECT causes significant damage to hippocampal or other brain tissue (Coffey *et al*, 1988; Devanand *et al*, 1994; Scott *et al*, 1995), or changes cognitive function greater than those produced by depression. Further, there were no grey matter difference between controls and the recovered patients, some of whom were on psychotropic medication and had previously received ECT. Also, ECT may be expected to produce prominent hippocampal atrophy, as it is the most vulnerable to the effects of seizure related hypoxia. However, there was no correlation between ECT and hippocampal grey matter in this study. This was underlined when the CTRD and RD groups were compared controlling for the number of ECT given- grey matter density reductions in the left hippocampus were still found in the CTRD group. Further, there was a positive correlation between total illness duration and bilateral hippocampi after controlling for cumulative severity. Because of this, and, as the total

number of ECT administered, total duration of in-patient stay and total number of hospitalisations were very closely intercorrelated it seemed reasonable to regard the total number of ECT administered as being an index of cumulative severity. However, the possibility of having a treatment, or ECT related effect cannot be finally discounted. Longitudinal studies are therefore required to determine whether cortical atrophy predates particularly severe illnesses which require ECT, or whether ECT causes such changes.

It could also argued that motor slowing was a consequence of repeated ECT particularly in those with later onset illnesses. However, later onset CTRD patients had not received more ECT than younger patients. Further, such enduring cognitive effect has not yet been reported in the literature. It is more likely that patients with motor retardation received ECT, this being a factor predicting a good response to ECT.

It could also be argued that the RD patients were still depressed. However, the RD group had insufficient symptoms to reach defining criteria for illness. Further, eighteen of the twenty had returned to work, the other two being unemployed not through the effect of illness and only of this group needed psychiatric follow-up, for medication monitoring purposes

only, suggesting symptomatic and functional recovery.

It could also be that the impairments seen were attributable to medication. Although none of the CTRD patients were drug free, about half of the recovered patients were medication free. There was no difference in symptoms or motor retardation between medicated and unmedicated recovered patients.

Finally, it may also be that the brain changes, as with dexamethasone suppression status, resulted from the effects of restricted food intake and weight loss, often exhibited by depressed patients. However, it is not clear why such changes should be localised or lateralised to the left side. Such considerations further emphasise the need for longitudinal studies.

5.5 Summary

1. Only patients with CTRD had changes in all three brain tissues in limbic and subcortical areas. RD patients and controls did not differ.
2. The CTRD patients had neocortical reductions in temporal and frontal regions, which correlated with the severity of illness over time, and therefore, possibly acquired.
3. The CTRD patients had right sided fronto-striatal atrophy, confirmed on conventional volumetric analysis, which was not present in the RD group. Both patient groups had age-related reductions in fronto-medial grey matter (Brodmann areas 9 and 10) which were also correlated with increasing severity of motor retardation in the CTRD group, and with age of onset in the RD group. The RD group continued to have residual motor retardation, despite good symptomatic, functional and social recovery. Thus, the results suggest that later onset depression, which show more endogenous features, is associated with acquired fronto-medial structural change, with clinical and structural features similar to a form of "sub-cortical" or "striato-frontal" dementia becoming more prominent with older age. There was some evidence that cumulative severity and older age interacted, so that the most pronounced fronto-medial reductions would be expected in the severely unwell, older

patients. Although similar results are found in the elderly depressed, these results suggest a relationship between structural change and age in a mainly middle aged group.

4. Hippocampal and rostral cingulate reductions were not related to cumulative severity, motor retardation, age of onset or to any of the other clinical factors measured. It may be that reduced grey matter density in these areas are markers for treatment resistance.
5. Other influences, such as cigarette smoking history may have pharmacological effects with secondary effects on cerebral water distribution.
6. The increased grey matter density in the precuneus could not be presently explained.
7. The form of voxel based analysis used in this study, SPM '96, provided a more detailed and anatomically precise examination of the MRI data. SPM analysis predicted right fronto-striatal atrophy in the CTRD group, which was confirmed on conventional volumetry. This effectively provides validity for SPM analysis

CHAPTER 6:

CHRONIC, TREATMENT RESISTANT DEPRESSION - MRI CORRELATES OF COGNITIVE IMPAIRMENTS.

CHAPTER 6: CHRONIC, TREATMENT RESISTANT DEPRESSION- MRI CORRELATES OF COGNITIVE IMPAIRMENTS.

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CHAPTER 6: CHRONIC, TREATMENT RESISTANT DEPRESSION - MRI CORRELATES OF COGNITIVE IMPAIRMENTS.

6.0 Abstract

The pattern of cognitive impairments often found with depression suggest temporal and frontal lobe dysfunction. Functional and structural imaging studies also suggest temporal and frontal dysfunction or atrophy, even on recovery, particularly in the elderly. The patients we examined with CTRD exhibited MRI changes in grey matter in frontal and left temporal regions. It is therefore possible that impaired cognitive function is associated with these structural changes and is a marker for chronicity.

The profiles of cognitive function of twenty patients with CTRD, twenty controls and twenty recovered patients were compared using a battery of neuropsychological measures. The scores from the neuropsychological tasks and the grey matter density of the different subject groups were correlated using voxel based analysis to localise impaired function to grey matter changes. Specifically, it was predicted that verbal memory impairment would be associated with reduced left temporal (hippocampal) grey matter density, and measures of motor retardation would be associated with reduced prefrontal grey matter density. An exploratory analysis was also performed of the clinical correlates of the cognitive impairments, to distinguish state

dependant, accumulative and age-related cognitive impairment.

Patients with CTRD were markedly impaired on verbal memory and psychomotor speed dependant tasks, suggesting a combined temporal and fronto-striatal functional deficit, but were also impaired on almost all other neuropsychological measures. They also showed a disparity between educational years and predicted premorbid IQ. Recovered patients showed significant slowing in reaction time measures only, compared to controls.

As predicted, impaired verbal memory was associated with reduced left hippocampal grey matter, and measures of psychomotor slowing were associated with diminished prefrontal cortex in the CTRD group. NART score also correlated with medial prefrontal cortex in the CTRD group only.

The exploratory analysis suggested that psychomotor slowing was associated with increasing age, current and cumulative illness severity in both patient groups. This suggests that the prefrontal grey matter changes associated with motor slowing were acquired and indicated an interaction between age and cumulative severity. A prospective, longitudinal study would be required to test this hypothesis.

The results help validate the differences in grey matter density found in the CTRD group, the differences being associated with the underlying dimension of function. The results also

challenge the notion that depression related cognitive impairment is fully reversible and suggest that it may be associated with an age related, acquired, prefrontal structural change, motor retardation being its manifestation.

6.1 INTRODUCTION

6.1.1 Background

Over the past fifteen years, a wealth of evidence has confirmed that even mild depression may be associated with cognitive deficits in several domains. Miller (Miller, 1975) reviewing the evidence, found that depression was associated with deficits in a number of domains including the cognitive, motor and perceptual. Further, Brown et al. (Brown *et al*, 1994), classifying depressed patients according to degree of global cognitive impairment into unimpaired, borderline or impaired groups, on the basis of performance on the CAMCOG (a measure of global cognitive function), found that even the unimpaired depressed patients showed clear cognitive deficits on sensitive measures of language, memory, attention and executive function compared to controls, and that global cognitive function and degree of neuropsychological impairment varied across the groups despite the three depressed groups having identical mean Hamilton depression rating scores. They concluded that cognitive dysfunction could not be considered as an "epiphenomenon of depressive symptomology" (Brown *et al*, 1994). Numerous studies thereafter have demonstrated a similar range of depression related cognitive deficits (Brown *et al*, 1994; Beats, 1996; Elliott *et al*, 1996; Austin *et al*, 1992a; Weingartner *et al*, 1981; Roy-Byrne *et al*, 1986; Austin *et al*, 1999).

6.1.2 The importance of cognitive impairment in depression

Depression associated cognitive impairment is important for a number of reasons. Firstly, although the exact causal relationship between neuropsychological impairment and depressive symptoms is unclear, it is known that neuropsychological impairment *per se* , is a risk factor for depression (Post, 1968; Devanand *et al*, 1996). This is illustrated when examining patients with suspected Alzheimer's disease- cognitive impairment can be sufficiently severe to make the differentiation between early Alzheimer's dementia and depression from clinical and neuropsychological profile difficult. Not only can dementia initially present with depressive symptoms, but a significant proportion of patients (up to 10%) initially thought to have an organic dementia, are later rediagnosed as having major depression (Huppert & Beardsall, 1993; a "pseudodementia" presentation). Thus, the type of marked cognitive impairment, once thought to be the hallmark of dementia, are frequently displayed by severely depressed elderly patients.

Secondly, enduring cognitive impairment may be an indicator of poor prognosis in a number of psychiatric illnesses. This is best established in schizophrenia (Breier *et al*, 1991; Gold & Harvey, 1993) where there is greater breadth of impairment compared to depression(Goldberg *et al*, 1993) associated with brain morphological changes (Goldberg *et al*, 1994).

The prognostic value of cognitive impairment in depression has been shown in the elderly (Harvey *et al*, 1997) and patients with bipolar affective disorder (MacKay *et al*, 1995). Harvey et al. (Harvey *et al*, 1997) for example, compared cognitive function in poor-outcome hospitalised geriatric patients with affective disorders and hospitalised patients with chronic schizophrenia and found no group differences, suggesting that severe cognitive impairment may characterise chronicity, regardless of diagnosis. Enduring impairment in the elderly depressed may be a marker of structural brain change potentially as a result of vascular disease. Such "organic" depressions appear to be associated with greater treatment resistance, greater morbidity and mortality. In younger patients too, impaired cognitive function may be associated with poor outcome (MacKay *et al*, 1995). Thus, if younger patients also exhibit pervasive cognitive impairment, it may argue in favour of structural brain change.

6.1.3 Characteristics of cognitive impairment in depression

Apart from mood change, severely depressed patients often prominently complain of lack of concentration, forgetfulness, lack of motivation and a physical and mental "slowing up", which can be as functionally disabling as pathological mood change.

These impairments are confirmed when patients perform

neuropsychological tests. Depressed patients exhibit prominent deficits in episodic memory, particularly verbal but also visuo-spatial memories (Austin *et al*, 1992a; Ilsley *et al*, 1994). Additionally, patients consistently demonstrate impairments on measures involving motor speed, decision making and problem solving (Austin *et al*, 1992a; Moffoot *et al*, 1994; Elliott *et al*, 1996), although the evidence for impairment in measures involving short term memory or attention is equivocal. Thus, patients demonstrate a wide range of cognitive deficit, and not a specific pattern attributable to the dysfunction of a single discrete neural system, making it difficult to offer a viable hypothesis explaining cognitive dysfunction both in terms of the biological substrate and psychological mechanisms.

The problem may be in suggesting a unitary neuronal system explantation encompassing the mood, motor and cognitive changes seen in depression. It would not be unexpected if the biological substrate for cognitive impairment differed in hospitalised elderly men, particularly with late onset depression whose depression may have a more vascular cause (Krishnan *et al*, 1997), than for out-patient middle aged women, whose depression may have a completely different aetiology. Motivational deficits, for example, has been advocated as a diagnosis-specific abnormality present even on recovery, producing cognitive impairment (Elliott *et al*, 1996; Elliott *et al*, 1997). However, this has not been

reproduced by others (Shah *et al*, 1999), possibly as a result of selecting depressed patients with differing clinical and aetiological characteristics, suggesting a diversity of mechanisms producing cognitive impairment.

6.1.4 Major depression and subcortical dementia

Neuropsychological deficits in depression have previously been conceptualised in terms of subcortical dementia. The cognitive impairments seen in basal ganglia disorders such as Parkinson's disease (PD) and Huntington's disease (HD), which form the archetype for subcortical dementia, have similarities with depression related cognitive impairment (Elliott *et al*, 1996), with problems with attention, bradyphrenia (ie slowed cognitive speed), problem solving difficulties, visuospatial abnormalities, and marked abnormalities of mood and affect being common to both (Cummings, 1986; Cummings, 1992). Both also differ from traditional cortical dementia (e.g. Alzheimer's disease) by the absence of aphasia and apraxia. Further, patients with PD and HD commonly develop depression (Cummings, 1992; Robbins *et al*, 1992), suggesting that disruption of frontro-striatal connections could lead to affect dysregulation. Hence it has been advocated that depression is associated with a fronto-subcortical or fronto-striatal dementia (Robbins *et al*, 1992).

6.1.5 Residual neuropsychological impairment on recovery from depression.

Considering that there may be structural brain change in depression, particularly fronto-subcortical, it is important to enquire if neuropsychological function completely normalises on recovery from depression. Full recovery would suggest that cognitive performance was state dependant, proportional to eg mood change. Further, if severity of depression and cognitive impairment were independent of each other, it may point towards different underlying neural substrates.

A number of studies have examined this, finding that motor speed tasks may be independent of mood (Moffoot *et al*, 1994), may not fully recover with symptomatic resolution (O'Brien *et al*, 1993) (Abas *et al*, 1990) and may be associated with structural change, particularly in the elderly (Abas *et al*, 1990). Moffoot et al. (Moffoot *et al*, 1994) examined the neuropsychological impairments in melancholically depressed in-patients during the 'trough' and 'peak' of their diurnal mood state. Measures of attention and concentration, working memory, and episodic memory varied with mood state, but impairment in motor speed tasks did not, suggesting that motor impairment may partially be independent of mood state and have a distinct neurobiological basis.

Abas et al. (Abas *et al*, 1990) examined elderly depressed patients

before and after recovery and found that recovery left some depressed patients (about 30%) with residual motor slowing and some memory impairment. Further, the residual cognitive impairment was significantly correlated with increased ventricular brain ratio measured on computerised tomography scans. The authors felt that the persisting impairments were not due to subclinical depression or possibly dementia, but suggested that repeated relapses were associated with increasing cognitive decline and increasing cerebral atrophy.

Finally, O'Brien (O'Brien *et al*, 1993) examined young (in their 30's), medication free patients with seasonal affective disorder (SAD) during and on recovery from depression, using the CANTAB. The scores on most tests improved on recovery, except on response latency to a spatial memory recognition task. This continued impairment correlated with the severity of residual depressive symptoms. However, unlike the elderly depressed patients in the study by Abas et al (Abas *et al*, 1990), no significant relationship was found between any measure of cognitive function and ventricular brain ratio.

Thus, it appears that, although most measures of cognitive function improve on recovery from depression, there may be residual cognitive impairment mainly in psychomotor speed but also some aspects of memory, and most prominently in the elderly. Such residual cognitive

impairments may be related to permanent changes in brain morphology, possibly in striato-frontal regions, particularly in elderly patients.

6.1.6 Aims of this study

The main aim of this study was to profile of neuropsychological deficits in CTRD and recovered patients and establish the functional associations of reduced grey matter density in the CTRD group - specifically, it was predicted that measures of episodic verbal memory would correlate with hippocampal grey matter, and measures of retardation (such as measures of reaction time) would correlate with basal ganglia and prefrontal grey matter. These correlations would effectively confirm the biological significance of any observed group differences, as these differences would then be not only categorical, but also related to the underlying dimensions of function.

The other aim was to explore the clinical correlates of neuropsychological impairments. The most consistent finding from previous studies is of fronto-striatal atrophy, and of enduring motor slowing even on recovery from depression, particularly in the elderly. However, it is not known if these changes are acquired, or preceded the development of illness. It may be that depression results in structural change reflected in residual slowing on recovery. If such an effect was accumulative, the degree of motor

slowing may be expected to reflect illness duration or cumulative severity, and be independent of current overall severity. Alternatively, if structural changes preceded the development of depression, neuropsychological measures may not be correlated with clinical variables. However, as this is a cross-sectional study, this analysis has to be regarded as exploratory.

6.2 Methods

6.2.1 Subjects, MRI technique and Statistical methods

Please see sections 5.2.1, 5.2.3 and 5.2.5 for details of the three groups examined, MRI sequences and statistical comparison methods. Group comparisons of neuropsychological test scores were identified using one-way ANOVA, with post-hoc t-tests for individual measures. Non- parametric correlations were performed between test scores and clinical variables as the clinical variables were not normally distributed.

6.2.2 Neuropsychological and clinical assessment

All subjects were interviewed using the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) (Endicott & Spitzer, 1978). All available casenotes were reviewed in detail, providing RDC diagnoses and allowing

lifetime histories of psychiatric illness to be determined. Treatment histories were re-constructed from casenotes and from interview. The total number of hospitalisations, cumulative length of psychiatric hospitalisation and cumulative number of ECT treatments were ascertained from case notes and were used as indices of cumulative illness severity.

All subjects underwent neuropsychological and clinical testing in a standardised environment, within a two day period. Symptom severity was measured using the HRSD (Hamilton, 1960) and the severity of psychomotor retardation using the observer rated Widlöcher scale (Widlöcher, 1983). Subjects also performed the following battery of neuropsychological tests in the order specified below:

1. Handedness scale (Annett, 1970): scoring between +24 (extreme righthandedness) and -24 (extreme lefthandedness).

2. Maximal voluntary contraction (MVC): Following Cohen et al (Cohen *et al*, 1982), who demonstrated that depressed patients exhibited motor performance deficits in proportion to the severity of depression, each subject squeezed a dynamometer as hard as possible. This was repeated three times for each arm. The three trial for each arm was averaged to give a measure of maximum voluntary

contraction.

3. National Adult Reading Test-Revised (NART, (Nelson & Willison, 1991)), a conventionally accepted reliable estimate of pre-morbid IQ.

4. The Adult Verbal Learning Test (AVLT (Rey, 1964; Lezak, 1983)); a test of new verbal learning ability, immediate and short term memory recall and recognition. A fifteen item list is presented verbally and needs to be recalled imediately after five consecutive repetitions. After 30 minutes free recall and recognition are both tested. The test minimises any possible effect of poor attention span by repeated presentations, and thus may be useful in depressed patients (Sweeney *et al*, 1989).

5. Digit span forwards and backwards (DSF, DSB): a test of concentration and immediate recall. This was presented and scored as in the Weschler Memory Scale-Revised (Wechsler, 1987).

6. Trails-making A and B (Army Individual Test Battery, 1944): this tests attention, concentration and psychomotor speed. Trails-B also requires the ability to shift cognitive set and is therefore more demanding a task.

7. The STROOP (ref) task, a measure of motor speed and of set shifting, and thus, of executive (frontal lobe) function.

8. Verbal Fluency (Borkowski *et al*, 1967): this task is regarded as a test of frontal lobe function and consists of generating as many words beginning with the letters F,A

and S as possible in 3 sixty second periods.

9. Reaction time tasks from the CANTAB computerised psychometric testing battery (Sahakian & Owen, 1992), which allow for a separate determination of the response initiation and movement times.

10. Simultaneous and delayed match to sample (SDMS) test from the CANTAB computerised psychometric testing battery (Sahakian & Owen, 1992); a measure of visuo-spatial memory also yielding measures of response latency to making a choice. This involves identifying the matching design to a complex pattern presented at four different times after the presentation of the index pattern.

6.3 Results

The comparison of demographic and clinical variables is shown in table 5.1 and has already been described in section 5.3.1.

6.3.1 Group comparison of neuropsychological test scores

Table 5.1 and 6.1 summarises the comparison of test scores.

6.3.1.1 NART score

Although the three groups were matched for years of eduction, the NART score was lower in the CTRD group compared to controls, with a trend difference compared with the recovered group. This was reflected in the correlational analysis- years of eduction and NART score were, as expected, closely correlated in the recovered and C groups, but were not in the CTRD group (Table 6.2).

6.3.1.2 Verbal memory and motor speed tasks

Overall, the CTRD group exhibited large impairments in almost all tests compared to both recovered and C groups, except in simple tests of concentration and attention (Digits forwards and backwards) and in the measure of effort or central motivational state (maximal voluntary contraction). The largest differences seen in the CTRD group were in verbal memory measures (AVLT) and measures explicitly involving response speed (reaction time, Stroop test, and Trails A and B). There were smaller impairments in the visuospatial memory task, the verbal fluency task and a test

Table 6.1: Group differences on performance on neuropsychological tasks.

	Treatment resistant (CTRD)	Recovered (RD)	Controls (C)	F-statistic (probability)	Post- hoc t-test
Digit span	(n=19)	(n=20)	(n=20)	$F_{2/58}$	
Digit span forward	8.1 (2.4)	8.8 (2.0)	9.1 (2.2)	1.3 (0.29)	
Digit span backward	6.5 (2.3)	7.2 (2.0)	7.1 (2.0)	0.6 (0.56)	
Maximal Voluntary Contraction	(n=18)	(n=20)	(n=20)	$F_{2/57}$	
Right arm	40.0 (13.2)	39.9 (10.8)	38.3 (14.7)	0.11 (0.90)	
Left arm	37.5 (9.8)	38.2 (10.4)	37.4 (12.3)	0.03 (0.97)	
Verbal memory	(n=19)	(n=20)	(n=20)	$F_{2/58}$	
AV5	9.68 (2.26)	12.4 (1.87)	13.1 (1.39)	18. 4 (<0.0001)	CTRD<RD,C
AVT	40.5 (13.5)	52.7 (8.3)	54.8 (7.7)	11.35 (0.0001)	CTRD<RD,C
AVB	4.68 (1.38)	5.55 (1.70)	6.55 (1.76)	6.4 (0.003)	CTRD<RD,C
AV6	8.05 (3.27)	11.45 (2.35)	11.1 (2.34)	9.4 (0.0003)	CTRD<RD,C
AVDL	8.16 (3.82)	11.35 (2.23)	11.1 (2.88)	6.62 (0.003)	CTRD<RD,C
AVRC	8.22 (4.82)	13.45 (1.36)	12.25 (2.81)	13.29 (<0.0001)	CTRD<RD,C
"Forgetting" (AV5-AVDL)	1.45 (3.0)	1.0 (1.8)	2.0 (2.6)	0.85 (0.43)	
Reaction time	(n=18)	(n=20)	(n=20)	$F_{2/57}$	
"Thinking" latency	670 (223)	549 (91)	483 (62)	8.6 (0.0006)	CTRD>RD>C

Table 6.1: Group differences on performance on neuropsychological tasks.

	Treatment resistant (CTRD)	Recovered (RD)	Controls (C)	F-statistic (probability)	Post- hoc t-test
Visuo-spatial memory	(n=13)	(n=17)	(n=19)	$F_{2/48}$	
MST (S)	8.9 (1.2)	9.4 (0.9)	9.5 (0.9)	1.45 (0.25)	
MST (0)	7.7 (2.0)	8.6 (1.2)	8.6 (1.0)	1.83 (0.17)	
MST (4)	7.3 (1.8)	8.6 (1.4)	8.7 (1.2)	4.20 (0.02)	CTRD<RD,C
MST (12)	5.9 (1.9)	7.4 (1.9)	7.4 (1.2)	4.02 (0.02)	CTRD<RD,C
MST (Total)	29.8 (5.6)	33.9 (4.1)	34.3 (2.6)	5.58 (0.007)	CTRD<RD,C
Stroop	(n=19)	(n=18)	(n=18)	$F_{2/54}$	
STRPW	111 (3.2)	112 (0)	112 (0)	0.9 (0.4)	
STRPP	21.5 (27.4)	58.5 (37.7)	70.8 936.0)	10.7 (0.0001)	CTRD<RD,C
STRPT	68.1 (23.0)	52.9 914.7)	53.4 (6.1)	5.2 (0.009)	CTRD>RD,C
STRPWC	35.6 (23.1)	11.8 (12.5)	8.8 (13.4)	12.9 (<0.0001)	CTRD>RD,C
Trails A and B	(n=19)	(n=20)	(n=20)	$F_{2/58}$	
Trails A	46.6 (17.4)	31.3 (12.0)	31.6 98.1)	8.8 (0.0005)	CTRD>RD,C
Trails B	111.3 (35.9)	66.5 (24.2)	59.3 (11.7)	23.3 (<0.0001)	CTRD>RD,C
Verbal fluency	(n=19)	(n=20)	(n=20)	$F_{2/58}$	
Total of three letters	36 (12.8)	44 (10.2)	48 (12.5)	5.2 (0.008)	CTRD<RD,C

of strategy (six elements test), thought to examine the integrity of the frontal lobes, where response speed was not important.

Table 6.2: Correlation between NART derived IQ and years of education.

	Years Education and NART IQ
CTRD	0.25 (0.15)
RD	0.72 (<0.001)
C	0.59 (0.003)

In verbal memory, the CTRD patients had impaired learning, delayed active recall of material and impaired passive recognition of words previously presented. The CTRD patients did not differ on the index of "forgetting" compared to both the recovered and C groups. Recognition was particularly impaired - there was better passive recognition than active recall in the recovered patients (13.4 (1.4) vs 11.3 (2.2); t= 5.29, p<0.001) and controls (12.2 (2.8) vs 11.1 (2.9); t= 2.71, p=0.01) groups, but not in the CTRD group (mean= 8.2 (SD=4.8) vs 8.1 (3.9); t=0.25, p=0.8).

The recovered patients did not differ in any of the neuropsychological measures except for reaction time, a relatively pure measure of motor retardation. Within the reaction time test, the greatest impairment in both CTRD and recovered groups was movement latency time. This was not related to medication status, as there was no difference in reaction time or any other motor speed or

memory related task between medicated and unmedicated recovered patients.

6.3.2 Exploratory correlation between grey matter density and neuropsychological measures.

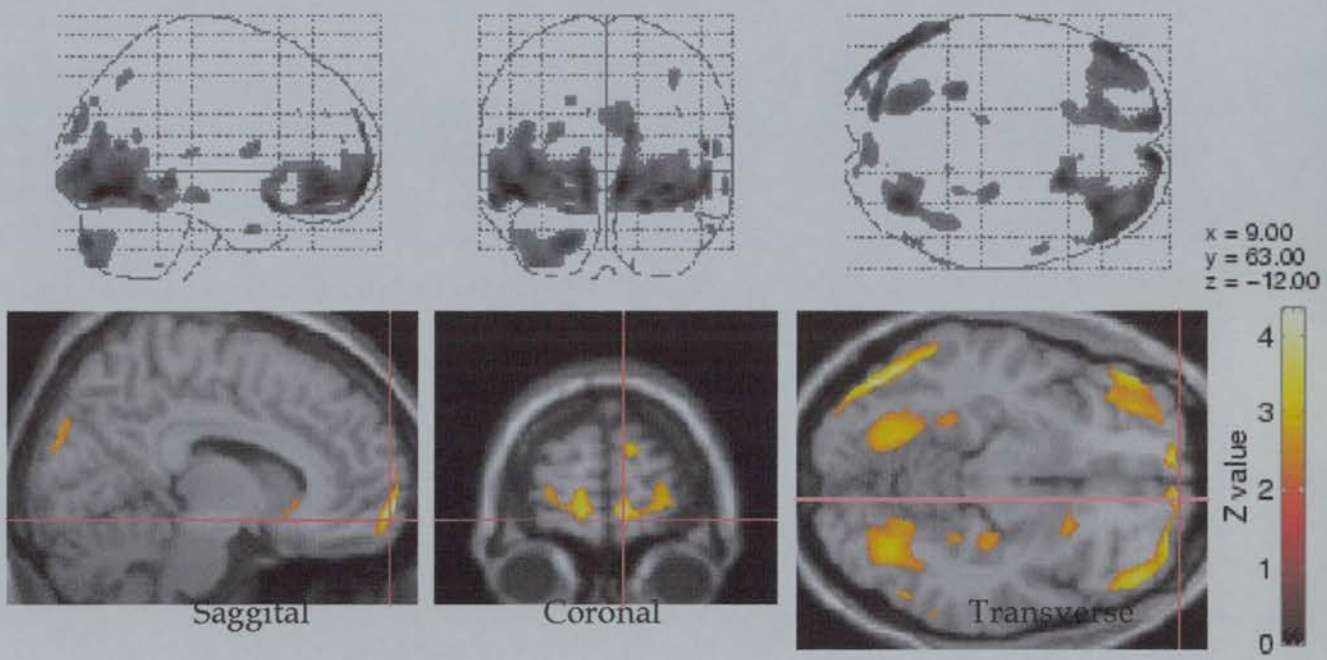
6.3.2.1 Correlation with NART score

NART score showed positive correlations with grey matter density in bilateral orbito-frontal/ medial frontal cortex and left occipital (figure 6.1), and a negative correlation with bilateral cerebellar grey matter density in only the CTRD and not the recovered and control groups. Because of the group difference in NART score, the grey matter group comparisons were repeated controlling for NART score (figure 6.2). The CTRD patients still had reduced grey matter density in left hippocampus and left temporal neocortex, compared to the combined recovered and C group, though the frontal neocortical reductions in grey matter density disappeared.

6.3.2.2 Correlation with verbal memory scores

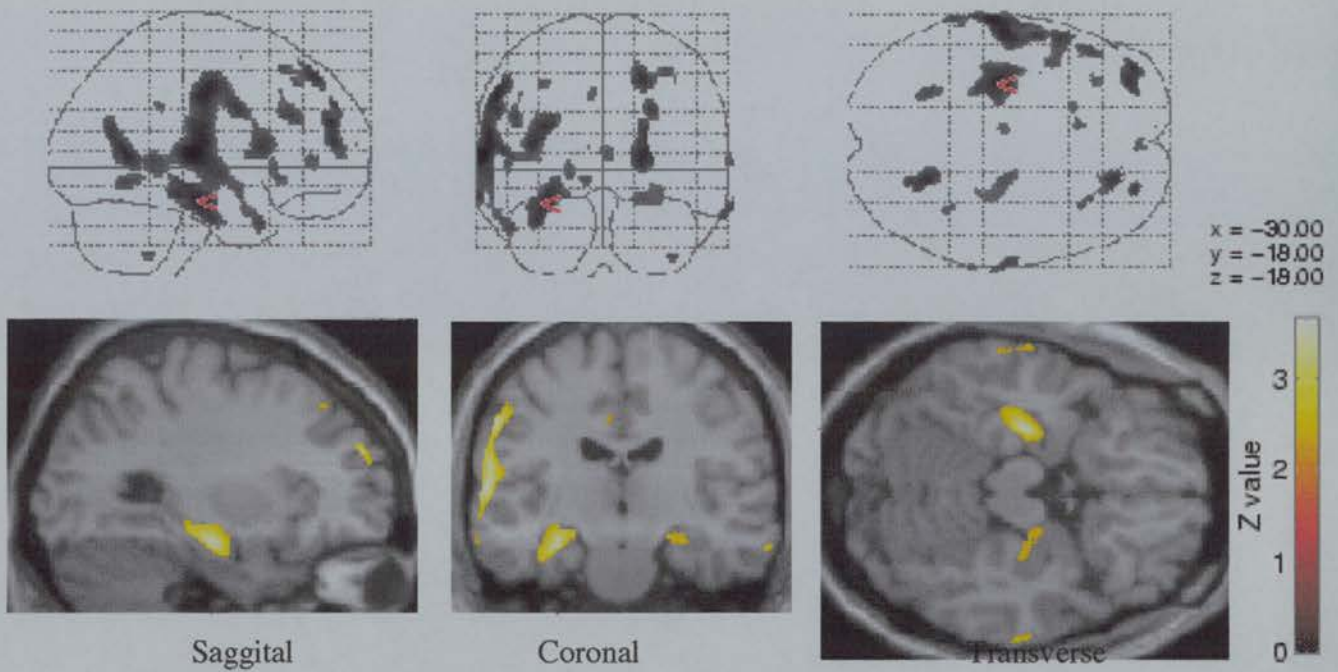
As predicted, verbal memory performance correlated with left hippocampal grey matter density in the CTRD group (figure 6.3). Delayed recognition from the AVLT was chosen, as it was particularly impaired in the CTRD group. Left hippocampal grey matter density was not related to the

Figure 6. 1. Positive correlation between grey matter density and NART score in CTRD.



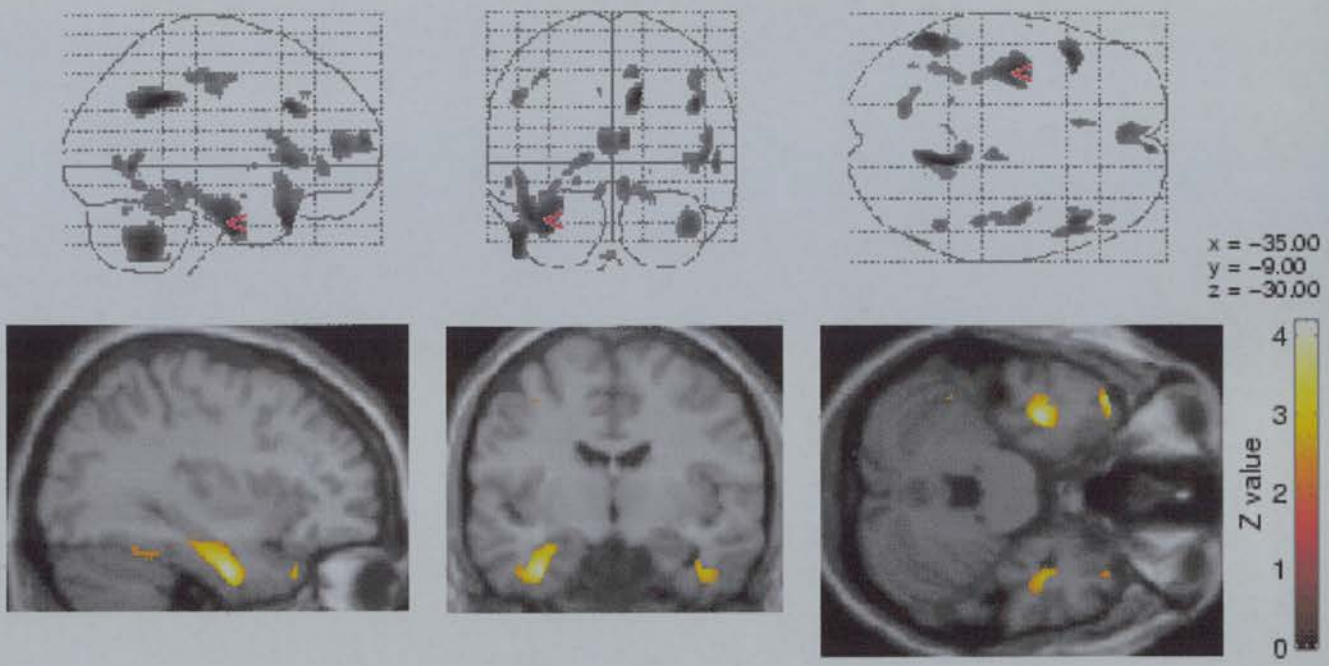
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
9,63,-6 (4.17)	<0.001 (0.18)	R. fronto-medial (10)	4629	<0.001 (0.02)
36, 35, -16 (3.77)	<0.001 (0.54)	R. infero-medial frontal (11/ 43)		
20, 14, -16 (3.76)	<0.001 (0.55)	R. inferior frontal (43)		
-46, -76, -10 (4.40)	<0.001 (0.08)	L. medial occipital (19)	4136	<0.001 (0.03)
-51, -68, -10 (4.24)	<0.001 (0.14)	L. medial occipital (19)		
-55, -62, -6 (3.86)	<0.001 (0.44)	L. medial occipital (19)		
-46, 43, -10 (3.69)	<0.001 (0.63)	L. fronto-medial (10/ 47)	2826	0.001 (0.09)
-12, 64, -2 (3.66)	<0.001 (0.66)	L. superior frontal (10)		
-11, 60, -12 (3.62)	<0.001 (0.71)	L. superior frontal (11)		
33, -70, -8 (4.0)	<0.001 (0.35)	R. medial occipital (19)	1946	0.006 (0.22)
22, -62, -10 (2.86)	0.002 (1.0)	R. lingual (19)		
42, -48, -16 (2.74)	0.003 (1.0)	R. fusiform (37)		

Figure 6.2. Reductions in grey density in the CTRD vs combined controls and RDs, controlling for the effects of age and NART score.



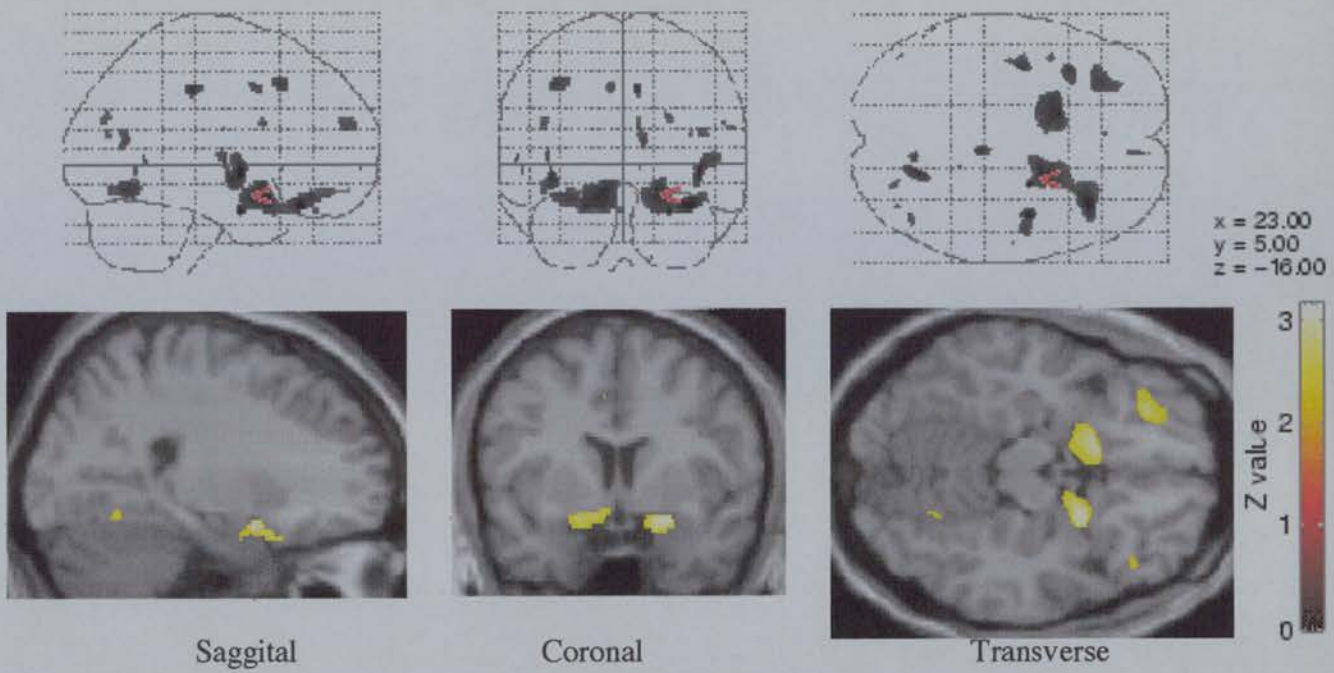
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-64, -23, 8 (3.81)	<0.001 (0.45)	L. superior temporal (42)	3626	<0.001 (0.039)
-57, -17, 38 (3.52)	<0.001 (0.78)	L. precentral (4)		
-60, -17, 14 (3.42)	<0.001 (0.86)	L. superior temporal (22)		
-30, -18, -18 (3.64)	<0.001 (0.65)	L. hippocampus	1622	0.011 (0.29)
-34, -14, -26 (3.16)	0.001 (0.98)	L. temporal pole (38)		
-27, -26, -10 (3.05)	0.001 (0.99)	L. hippocampus		

Figure 6.3. Positive correlations between grey matter density and AVRC score (delayed recognition of previously learnt words), controlling for age and NART score.



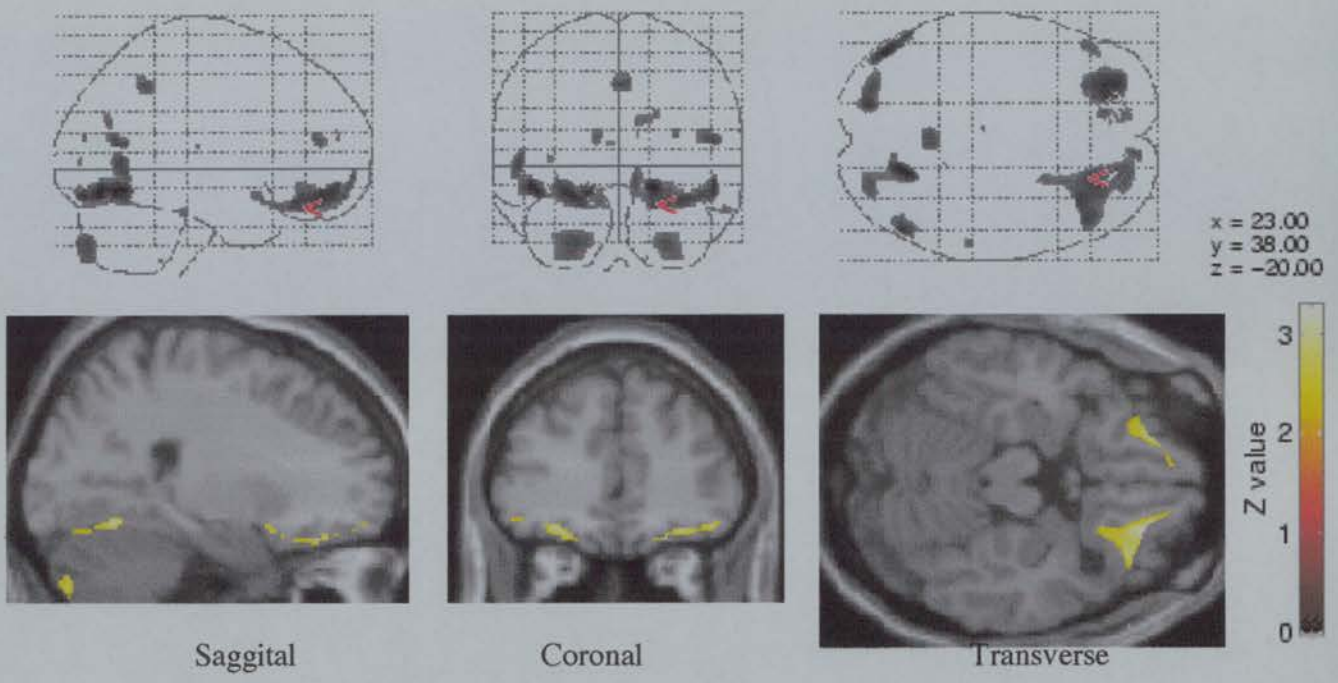
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
-35, -9, -30 (4.19) -32, -28, -14 (2.70)	<0.001 (0.16) 0.003 (1)	L. inferior temporal (20) L. hippocampus	1741	0.009 (0.25)

Figure 6.4. Negative correlations between grey density and total reaction time in CTRD.



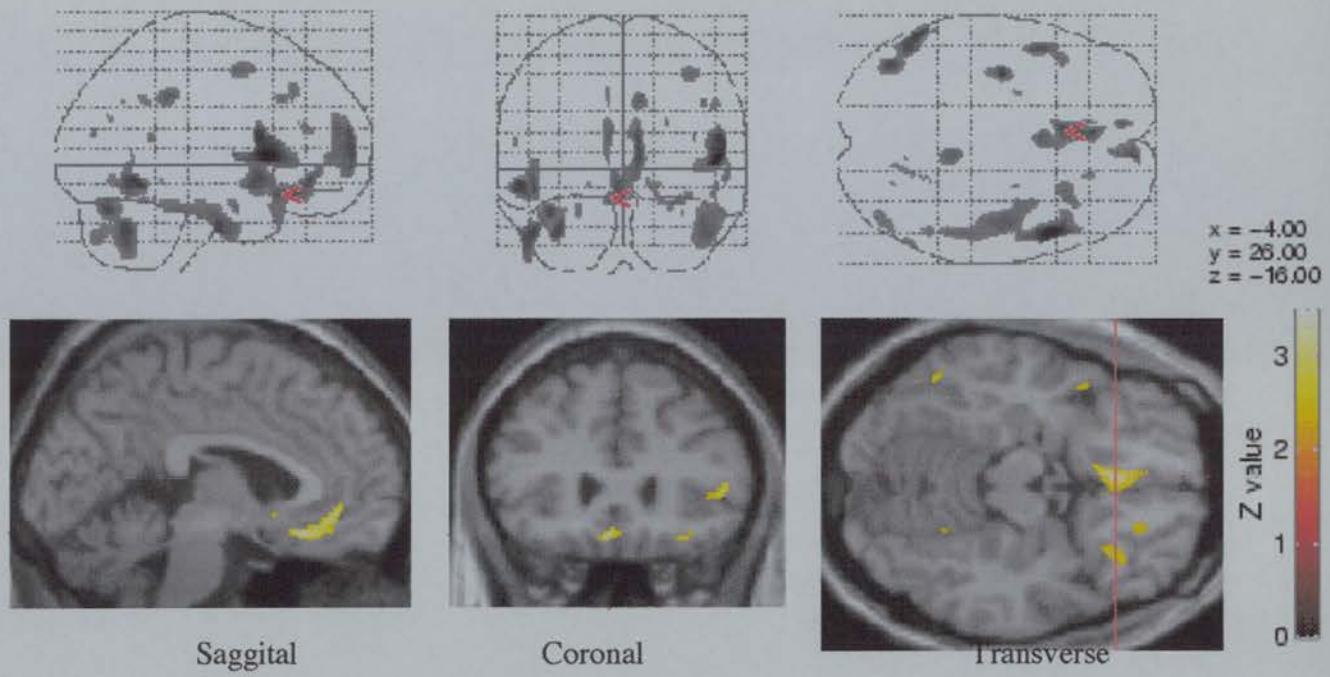
Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
26, -3, -24 (3.51)	<0.001 (0.81)	R. parahippocampal (35)	1461	0.017 (0.42)
36, 29, -20 (3.43)	<0.001 (0.88)	R. inf. frontal 47)		
23, 5, -16 (3.16)	0.001 (0.99)	R. inf. frontal (47)		
-10, 10, -12 (3.13)	0.001 (0.99)	L. subcallosal ant. cing. (25)	1306	0.022 (0.49)
-20, 11, -20 (2.99)	0.001 (0.99)	L. inf. frontal (47)		

Figure 6.5. Negative correlations between grey density and total reaction time in CTRD controlling for age.



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
23, 38, -20 (3.29)	<0.001 (0.95)	R. sup. and med. frontal (11)	1570	0.013 (0.36)
34, 31, -18 (3.29)	0.001 (0.96)	R. sup. and med. frontal (11)		
44, 35, -16 (3.28)	0.001 (0.96)	R. sup. and med. frontal 11)		
-25, 46, -16 (3.64)	<0.001 (0.67)	L. medial frontal (11)	853	0.06 (0.74)
-10, 55, -18 (2.68)	0.004 (1)	L. superior frontal (11)		
-15, 42, -22 (2.48)	0.007 (1)	L. medial frontal (11)		

Figure 6.6. Negative correlations between grey density and Trails B time in CTRD, controlling for age.



Co-ordinates of peak voxels (Z-statistic)	uncorrected p-value (corrected)	Anatomical region (Broadmann area)	size of cluster (voxels)	uncorrected p-value (corrected)
52, 14, 6 (4.67)	<0.001 (0.025)	R. inf. frontal/ sup. temporal	1407	0.018 (0.072)
53, 12, 16 (3.94)	<0.001 (0.35)	R. inf. frontal/ sup. temporal		
53, 5, 4 (3.17)	0.001 (0.99)	R. inf. frontal/ sup. temporal		
-4, 24, -16 (3.49)	<0.001 (0.83)	L. medial frontal (25)	964	0.044 (0.71)
-3, 37, -10 (3.33)	<0.001 (0.94)	L. medial frontal (25)		
1, 10, -6 (3.09)	0.001 (0.99)	R. medial frontal (25)		
9, 61, 10 (3.42)	<0.001 (0.88)	R. medio-frontal (10)	839	0.058 (0.79)
8, 59, 18 (3.27)	0.001 (0.96)	R. medio-frontal (10)		
7, 60, -2 (2.98)	0.001 (0.99)	R. medio-frontal (10)		

Table 6.3: Clinical correlations of performance on neuropsychological tasks in the CTRD group

	HDRS	Widlocher score	Age	Age first onset	Age onset last episode	Number of ECT	No. Past hospitalisations	Total duration hospitalisation
NART IQ	0.08 (0.372)	0.03 (0.456)	0.18 (0.235)	-0.2 (0.47)	0.06 (0.41)	-0.27 (0 .131)	-0.17 (0.24)	0.06(0.41)
Verbal memory								
AV5	-0.25 (0.15)	-0.17 (0.24)	0.27 (0.13)	0.33 (0.08)	0.15 (0.27)	**-0.53 (0.01)**	**-0.4 (0.03)**	-0.30 (0 .1)
AVDL	0.01 (0.48)	-0.17 (0.25)	0.17 (0.24)	0.12 (0.31)	0.13 (0.30)	-0.28 (0.13)	-0.29 (0.11)	-0.16 (0.25)
AVRC	-0.24 (0.17)	-0.25 (0.15)	0.09 (0.36)	0.09 (0.36)	0.01 (0.49)	**-0.56 (0.009)**	**-0.62 (0.003)**	**-0.45 (0.029)**
Reaction time								
"Thinking" latency	**0.5 (0.016)**	**0.48 (0.022)**	0.34 (0.087)	**0.43 (0.04)**	**0.44 (0.03)**	0.18 (0.23)	-0.06 (0.41)	-0.07 (0.40)
Movement latency	**0.48 (0.025)**	**0.41 (0.05)**	0.37 (0.07)	0.35 (0.09)	**0.39 (0.06)**	-0.02 (0.46)	-0.02 (0.46)	-0.01 (0.49)
Total latency	**0.52 (0.01)**	**0.48 (0.022)**	0.36 (0.07)	**0.37 (0.06)**	**0.46 (0.03)**	0.13 (0.31)	-0.02 (0.47)	-0.025 (0.46)
Visuo-spatial memory								
MST (total)	-0.30 (0.16)	**-0.46 (0.056)**	0.17 (0.29)	0.32 (0.14)	0.11 (0.36)	-0.26 (0.20)	-0.16 (0.31)	-0.024 (0.47)
Stroop								
STRPP	**-0.60 (0.003)**	**-0.63 (0.002)**	0.10 (0.35)	-0.04 (0.44)	0.02 (0.45)	**-0.51 (0.01)**	-0.25 (0.15)	**-0.40 (0.05)**
STRPT	**0.51 (0.01)**	**0.54 (0.01)**	0.33 (0.08)	0.23 (0.17)	**0.40 (0.05)**	0.33 (0.08)	0.10 (0.34)	0.09 (0.35)
STRPWC	**0.55 (0.007)**	**0.45 (0.025)**	0.30 (0.1)	-0.22 (0.19)	0.34 (0.07)	0.32 (0.09)	0.13 (0.30)	0.19 (0.22)
Trails								
Trails A	**0.66 (0.001)**	**0.46 (0.023)**	**0.51 (0.012)**	**0.44 (0.03)**	**0.52 (0.01)**	0.26 (0.14)	0.12 (0.31)	0.06 (0.40)
Trails B	**0.52 (0.011)**	**0.46 (0.024)**	**0.41 (0.04)**	0.20 (0.21)	**0.51 (0.01)**	**0.38 (0.05)**	0.32 (0.09)	0.19 (0.22)
Verbal fluency	-0.33 (0.08)	-0.32 (0.09)	-0.08 (0.38)	-0.13 (0.29)	-0.11 (0.33)	**-0.39 (0.05)**	-0.29 (0.11)	-0.09 (0.36)
Six element test								
Number of tasks	**0.56 (0.02)**	0.31 (0.14)	0.005 (0.49)	0.03 (0.47)	0.03 (0.47)	0.41 (0.07)	0.44 (0.06)	0.25 (0.19)
Number of rule breaks	**0.45 (0.05)**	**0.47 (0.05)**	0.12 (0.34)	-0.15 (0.30)	0.04 (0.44)	**0.45 (0.05)**	0.44 (0.06)	0.22 (0.22)
overall score	0.38 (0.09)	0.04 (0.44)	0.19 (0.26)	0.18 (0.27)	0.32 (0.13)	0.03 (0.45)	0.06 (0.42)	0.05 (0.44)

Table 6.4: Clinical correlations of performance on neuropsychological tasks in the RD and Control groups.

RDs	HDRS	Widlocher score	Age	Age first onset	Age onset last episode	Number of ECT	No. Past hospitalisations	Total duration hospitalisation
Verbal Memory								
AV5	-0.12 (0.30)	-0.02 (0.47)	-0.23 (0.16)	-0.31 (0.09)	-0.34 (0.07)	**-0.45 (0.023)**	-0.09 (0.30)	-0.13 (0.30)
AVDL	-.030 (0.10)	-0.36 (0.059)	**-0.58 (0.003)**	**-0.44 (0.02)**	**-0.65 (0.001)**	-0.26 (0.13)	0.04 (0.43)	0.08 (0.37)
AVRC	-0.02 (0.47)	-0.19 (0.21)	-0.05 (0.41)	-0.28 (0.12)	-0.13 (0.29)	-0.26 (0.13)	0.15 (0.26)	0.33 (0.09)
Reaction time								
"Thinking" latency	0.23 (0.17)	0.20 (0.20)	**0.45 (0.02)**	**0.45 (0.02)**	**0.51 (0.01)**	0.31 (0.09)	**0.36 (0.057)**	**0.69 (0.001)**
Movement latency	0.20 (0.20)	**0.39 (0.05)**	0.27 (0.13)	0.25 (0.14)	0.23 (0.16)	**0.57 (0.004)**	**0.48 (0.02)**	**0.39 (0.05)**
Total latency	0.25 (0.15)	0.25 (0.14)	**0.40 (0.04)**	**0.39 (0.05)**	**0.46 (0.02)**	**0.36 (0.057)**	**0.44 (0.027)**	**0.70 (0.001)**
Stroop								
STRPP	-0.17 (0.25)	-0.19 (0.23)	-0.35 (0.08)	**-0.49 (0.02)**	**0.39 (0.05)**	**-0.50 (0.02)**	-0.29 (0.12)	-0.23 (0.20)
STRPT	0.10 (0.35)	0.11 (0.33)	**0.37 (0.06)**	**-0.61 (0.004)**	**0.44 (0.03)**	**0.48 (0.02)**	0.10 (34)	0.06 (0.41)
STRPWC	0.23 (0.17)	0.16 (0.26)	**0.55 (0.009)**	**0.47 (0.03)**	**0.58 (0.006)**	**0.49 (0.019)**	0.32 (0.1)	0.30 (0.13)
Trails								
Trails A	0.08 (0.37)	0.30 (0.10)	**0.49 (0.015)**	0.31 (0.09)	**0.51 (0.01)**	**0.52 (0.009)**	0.20 (0.2)	0.24 (0.17)
Trails B	**0.44 (0.027)**	0.36 (0.06)	**0.40 (0.04)**	**0.44 (0.03)**	**0.43 (0.03)**	**0.44 (0.025)**	0.34 (0.07)	**0.42 (0.04)**
Verbal fluency	-0.05 (0.41)	-0.19 (0.21)	-0.04 (0.43)	-0.22 (0.18)	-0.11 (0.32)	0.07 (0.38)	-0.07 (0.39)	-0.19 (0.23)
Six element test total score	0.32 (0.10)	-0.01 (0.48)	0.15 (0.27)	0.13 (0.30)	-0.11 (0.32)	-0.25 (0.16)	0.11 (0.34)	0.20 (0.23)

Cs	Widlocher score	Age
Reaction time		
"Thinking" latency	0.06 (0.39)	0.01 (0.48)
Movement latency	0.17 (0.24)	-0.26 (0.13)
Total latency	0.05 (0.41)	-0.04 (0.43)
Stroop		
STRPP	-0.11 (0.33)	0.01 (0.48)
STRPT	0.06 (0.41)	-0.15 (0.27)
STRPWC	0.08 (0.37)	0.06 (0.41)
Trails		
Trails A	0.1 (0.34)	0.35 (0.06)
Trails B	0.21 (0.18)	0.36 (0.06)
Verbal fluency	0.26 (0.14)	0.1 (0.34)
Six element test total score	0.04 (0.4)	0.2 (0.2)

the number of ECT previously administered (see section 5.3.3.2).

6.3.2.3 Correlation with measures of motor speed

There was a negative correlation between total reaction time and right orbito-frontal cortex in the CTRD group (figure 6.4) but no correlation in both the controls and recovered patients. This negative correlation remained after controlling for age (figures 6.5). Time taken for the Trails B task in the CTRD group negatively correlated with grey matter density in right inferior frontal/ superior temporal cortex (figure 6.6).

6.3.3 Clinical correlations of neuropsychological measures

Tables 6.3 and 6.4 show the Spearman correlations between neuropsychological task scores and clinical variables in the three groups.

6.3.3.1 Clinical correlations of NART score

In the CTRD group, NART score correlated with none of the clinical variables, including cumulative severity (number of ECT) and total duration of illness, and was not related to the current severity of depression or retardation.

6.3.2.2 Clinical correlations of verbal memory (table 6.3 and 6.4)

In the CTRD group, the most impaired verbal memory measures, delayed recognition (AVRC) and verbal learning (AV5),

were negatively correlated with measures of cumulative severity (number of ECT, and number of hospitalisations) and not with current symptom severity. The recovered group showed no impairment in verbal memory and no correlation with residual symptom severity or motor retardation.

6.3.2.3 Clinical correlations of motor speed dependant tasks (table 6.3 and 6.4)

In both the CTRD and recovered groups, measures with explicit motor speed demands (reaction time, Stroop, and Trails tasks) correlated with clinically rated motor retardation (Widlocher score), thus providing validity for the Widlocher scale. In both groups, motor tasks also correlated with the HRSD score and the number of ECT previously administered, suggesting that motor slowing reflected both current and cumulative illness severity.

Performance on motor speed tasks slowed with age in both patient groups, but not in controls. Greater motor slowing was also associated with older age at onset of first and last episodes. Age and age at first onset were positively correlated in both patient groups, suggesting older patients in this study had had a later first onset of illness. Thus, the results suggest that both a later onset of illness, and a more severe illness, contribute towards greater residual slowing on recovery.

6.4 Discussion

6.4.1 Main findings

The main findings of this study were that:

a. Patients with CTRD had severe neuropsychological impairments, particularly in episodic verbal memory and motor speed tasks. As predicted, verbal memory impairment correlated with reduced left hippocampal grey matter density, and measures of motor slowing correlated with prefrontal grey matter reduction. The results thus support the notion that medial temporal and fronto-striatal function is impaired in chronic depression and, suggest that the functional correlate of right prefrontal atrophy found in the CTRD patients is motor retardation.

b. Recovered patients had residual motor retardation, measured clinically and objectively (using the reaction time measure), but did not have fronto-striatal atrophy. The degree of slowing was not related to medication.

c. CTRD patients had a reduced NART score, which correlated with reduced medial prefrontal grey matter density, suggesting performance on the NART was sensitive to focal grey matter changes.

d. An exploratory analysis suggested that the degree of verbal memory impairment in the CTRD group reflected the cumulative severity of illness and not current severity of symptoms. The degree of motor slowing on relatively pure measures of speed reflected the current severity of

symptoms, cumulative illness severity and older age in both patient groups. NART score did not correlate with any clinical factor.

e. The form of voxel based analysis used, SPM'96, was a valid form of analysis in correlating structure with function on T1-weighted MRIs.

6.4.2 Pattern of neuropsychological impairments

The chronic, treatment resistant depressed patients were particularly impaired on episodic verbal memory tasks and tasks involving psychomotor speed, but showed neuropsychological impairments on almost all tasks, except in those measuring attention, concentration and motor effort. They also exhibited a disproportionate reduction in NART score compared to that expected on the basis of their educational years.

6.4.2.1 Verbal memory

Delayed recognition of previously learnt verbal material was the most impaired verbal memory measure. Recent studies have found that verbal recognition is impaired in depression, particularly in those with melancholic symptoms (Austin *et al*, 1992a; Austin *et al*, 1999), memory impairment being proportional to the severity of depression. There is also evidence that verbal memory is dependent on the integrity of the temporal lobe.

Recognition has been found to depend on intact temporal lobe function, whereas recall depends on working memory, a pre-frontal cortical function (Goldman-Rakic, 1995). Lesion experiments in animals (Squire, 1992; Squire *et al*, 1992) and clinical studies (Baxendale, 1997; Mayes & Downes, 1997) also indicate the need for temporal integrity for memory function.

6.4.2.2 Motor slowing

The CTRD patients showed prominent motor slowing on all tests involving speed. However, only the reaction time task was impaired in both patient groups, a task which has previously been found to be a sensitive measure of motor retardation (Shah *et al*, 1996). Further, of all the neuropsychological tasks involving motor speed, it most closely reflected the severity of clinically rated motor retardation (Widlocher score) and symptoms in both patient groups. The results suggest that the reaction time task may be a sensitive measure of psychomotor retardation. Hence, it is not unexpected that, of all the neuropsychological measures, reaction time measures correlated with reduced prefrontal cortex.

The reaction time task was also the only one in which recovered patients continued to be impaired, the degree of impairment correlating with the clinically rated measure of motor retardation. This is in keeping with previous

evidence which has shown recovered patients to have residual slowing after recovery from depression (O'Brien *et al*, 1993) (Abas *et al*, 1990). Interestingly, structural change in recovered patients has been found only in the elderly (O'Brien *et al*, 1993) (Sheline *et al*, 1996)- we found no significant structural differences in our sample of middle-aged recovered patients.

The results of the exploratory correlational analysis were in keeping with the findings outlined in chapter 5- objective measures of motor slowing in both patient groups, particularly reaction time, reflected both the current severity of depressive symptoms, cumulative severity and age (see section 5.4.3 (B) for further discussion). The conclusions from this analysis have to be considered as hypothesis generating, given the relatively small numbers of subjects in the groups in comparison to the number of comparisons made.

6.4.2.3 Premorbid IQ

Although the groups were matched for total number of years in full time education, the CTRD group showed a mismatch between educational years and predicted premorbid IQ derived from the NART score. As NART scores and educational years are usually closely correlated, and as the NART score reduction in the CTRD group was unrelated to any of the clinical factors, it suggests a non-progressive,

acquired effect. NART scores are traditionally regarded as being resistant to pathologies associated with general intellectual decline and has become the standard measure of premorbid IQ. However, there is evidence that NART scores may be dispropotionately reduced in patients with melancholic depression and may be sensitive to focal brain changes. Austin et al (Austin *et al*, 1999) examined a large sample of depressed patients referred to a specialised mood disorders clinic and found that patients with melancholic depression had a lower NART derived premorbid IQ than non-melancholic patients, despite being matched for years education. Further, in patients with chronic schizophrenia, who also exhibit broad cognitive impairment, NART may not accurately measure premorbid IQ (Crawford *et al*, 1992) and may be affected by left temporal lobe atrophy. Also, patients particularly with left temporal lobe tumours (Ebmeier *et al*, 1993) also exhibit a dissociation between educational years and NART scores. The present results suggest that NART score may also be sensitive to changes in medial prefrontal cortex, which is part of the "dorsal cognitive loop" involved in the regulation of a number of executive functions.

6.4.3 Grey matter correlations

Although episodic verbal memory and tasks involving motor speed were equally impaired, deficits in these tasks mapped to

different areas of the brain- verbal memory impairment was associated with left hippocampal grey matter changes, and motor slowing was associated with prefrontal grey matter.

Thus, the results suggest that a pure fronto-striatal dementia model may be insufficient to account for all the cognitive deficits seen in depression. This is in broad agreement with the findings from previous functional neuroimaging studies (Bench *et al*, 1993; Curran *et al*, 1993; Dolan *et al*, 1993) which find both frontal and temporal hypoperfusion during depression, and neuropsychological studies (Elliott *et al*, 1996; Austin *et al*, 1992a; Austin *et al*, 1999; Greenwald *et al*, 1996) which show both mnemonic and psychomotor impairments, again suggesting frontal and temporal lobe impairment. Elliott et al (Elliott *et al*, 1996), for example, tested the fronto- subcortical dementia hypothesis by comparing the neuropsychological profile of depressed patients with Alzheimer's disease, PD and HD using the CANTAB battery of neuropsychological tests. As the depressed patients were impaired on almost all tests, they concluded that the impairments may be attributable to combined fronto-striatal and temporal dysfunction. Austin et al (Austin *et al*, 1992a) examined forty depressed patients dichotomised into endogenous and neurotic groups on the basis of the Newcastle score. They found that patients with an endogenous symptom profile were particularly impaired

on tests involving motor or cognitive speed. They also found the depressed patients exhibited memory impairment, suggesting medial temporal lobe involvement.

Fronto-subcortical dementia pattern may not be present in all depressed patients. Massman et al. (Massman *et al*, 1992) used discriminate function analysis to compare the neuropsychological profile of patients with unipolar depression, bipolar depression, Huntington's disease, Alzheimer's disease, and normal controls. About half the depressed patients had a normal memory profile, 30% a subcortical dementia profile, and none a cortical dementia profile. The patients with a subcortical dementia pattern were most impaired on speed-dependent information processing tasks such as the WAIS-R Digit Symbol Score, Digit Symbol Incidental Recall Score, Trail Making B performance, and Category Fluency, ie tests in which patients with subcortical dementia have significant impairment.

Greenwald et al (Greenwald *et al*, 1996) reported left medial temporal atrophy to be correlated with cognitive impairment in late onset depression, and Ebmeier et al (Ebmeier *et al*, 1997; Ebmeier *et al*, 1998) reported reduced left temporal perfusion in late onset depression. Finally, correlation of left hippocampal volume with verbal memory performance has been found in patients with schizophrenia (Goldberg *et al*, 1994), who also have reduced hippocampal size (Suddath

et al, 1990; Lawrie & Abukmeil, 1998; Velakoulis *et al*, 1999). Functional imaging studies have so far only provided equivocal evidence (Fletcher *et al*, 1997).

Thus, fronto-subcortical involvement in depression may be most applicable to patients exhibiting an endogenous symptom profile with prominent psychomotor impairment, as has been found in this study, with temporal lobe involvement being present in patients with significant cognitive or memory impairment.

6.4.4 Structural changes, chronicity and cognitive impairment

As the hippocampal changes were found only in the CTRD group, and were associated with reduced episodic verbal memory, it suggests that memory impairment may be a risk factor for (continuing) poor outcome.

There is supportive evidence from the literature that cognitive impairment is associated with chronicity- McKay et al. (McKay *et al*, 1995) have found that patients with chronic bipolar affective disorder suffer substantial cognitive impairment. Harvey et al. (Harvey *et al*, 1997) found no difference in cognitive function between poor-outcome hospitalised geriatric patients with affective disorders and hospitalised patients with chronic schizophrenia, suggesting that chronic illness may be associated with severe cognitive impairment, regardless of diagnosis. Importantly, their

patients with chronic affective disorder suffered comparable levels of negative symptoms as younger patients with chronic schizophrenia, suggesting an overlap of symptoms common to chronicity in both conditions.

There are also parallel findings in patients with other chronic psychiatric diagnoses. Hippocampal atrophy has also been found in patients with schizophrenia (Woodruff *et al*, 1997; Lawrie & Abukmeil, 1998; Velakoulis *et al*, 1999) as well as in severe PTSD (Bremner *et al*, 1995). Thus, it has been suggested that left hippocampal changes may be markers of chronicity, regardless of diagnosis (Velakoulis *et al*, 1999). Interestingly, left hippocampal volume may be reduced in patients with first-episode psychosis (Velakoulis *et al*, 1999), suggesting the presence of a neurodevelopmental abnormality. The results of this present study also show the left hippocampal grey matter changes are not related to illness duration or severity, although verbal memory impairment was worse with increasing cumulative illness severity. Clearly, the aetiological relationship between memory impairment, hippocampal changes and chronicity cannot be resolved in a cross-sectional study such as the present one, and requires longitudinal study.

6.4.5 Correlational analysis using SPM'96 provided valid results

The pattern of correlation of grey density reductions with cognitive

impairments were consistent with findings from previous functional and structural imaging studies (Bench *et al*, 1993; Dolan *et al*, 1993; Curran *et al*, 1993) and help validate the use of this form of voxel based analysis in analysing MRI images. The validity of voxel based analysis in analysing MRI images has also been shown in a study by Wright et al (Wright *et al*, 1995) who were able to reproduce the findings from volumetric analysis in a sample of patients with schizophrenia. The form of voxel based analysis used here (SPM '96) is more sophisticated than the one used by Wright et al (SPM '95) (Wright *et al*, 1995) as tissue densities in the latter had binary values (0 or 1), whereas in this study, the range of signal intensities was preserved, with density values ranging from 0 to 1). It is, therefore likely that voxel based analysis may be usefully employed in analysing MRI images, and may provide a more complete and sensitive analysis than traditional volumetry.

6.4.6 Limitations of study

A limitation of the study, is that it was cross-sectional in design. Thus, although the clinical correlations of cognitive impairments may provide clues as to whether the impairments were acquired, accumulative or trait dependent, the exact causal relationship cannot ultimately be ascertained in this study, emphasing the need for longitudinal studies.

A further criticism of the study could be the lack of correction for multiple comparisons in the correlational analysis between neuropsychological and clinical measures. This part of the analysis has to be regarded as exploratory and aimed to generate as opposed to testing hypotheses. Nevertheless, the relationship between both clinically rated and objectively measured motor retardation, medial frontal cortex and age or age of onset is robust, and consistent with the established evidence, as is the relationship between episodic verbal memory and left hippocampus. However, further studies would be needed to directly test the hypotheses generated by this study.

A final criticism is the relatively small numbers involved in each group. Small group size would increase the likelihood of a type 2 error ie. incorrectly accepting the null hypothesis. In this circumstance, only large differences or strong associations would be detected.

6.5 Summary

1. Patients with CTRD showed marked impairments in episodic verbal memory, speed dependant cognitive tasks and measures of general cognitive ability compared to both controls and recovered patients. They were also impaired in tasks of executive function to a lesser degree, but not impaired in measures of attention and working memory.
2. Impaired episodic verbal memory correlated, as predicted, with left hippocampal grey matter density, thus providing validity for the group difference, as it correlated with underlying function. Hippocampal grey matter change and verbal memory impairment were found only in the CTRD group. Thus, hippocampal change may be markers for chronicity, a conclusion supported by similar findings in patients with chronic schizophrenia.
3. Objectively measured motor slowing correlated, as was predicted from the existing evidence, with reduced grey matter in inferior prefrontal cortex. The relationship between clinically rated retardation, age and prefrontal cortex was broadly reproduced using objective measures of retardation in both patient groups. Patients who had recovered from depression were impaired on reaction time measures which were the most sensitive to motor retardation. The results are in concordance with the findings from chapter 5.

4. NART scores were dispropotionately reduced in the CTRD group

compared to that expected on the basis of years of education. This reduction correlated with reduced grey matter density in medial prefrontal cortex, implicating this area in broader, cognitive processes.

5. The particular type of voxel based analysis used, SPM'96, produced results localising episodic verbal memory and motor slowing to left hippocampus and inferior prefrontal cortex respectively, as was predicted on the basis of the existing literature. This provides validity for the use of voxel based analysis in analysing MRI data.
6. There are striking similarities in the cognitive deficits in patients with chronic depression and chronic schizophrenia, together with a convergence in the brain areas involved in the pathology of both conditions. It therefore suggests a common pathway to chronicity, regardless of diagnosis

CHAPTER 7:

CONCLUSIONS

CHAPTER7: CONCLUSIONS

7.1 Overview

The thesis starts by reviewing evidence from recent functional imaging studies which confirm that limbic and subcortical structures are involved in the neurobiology of depression. The areas include striatal, frontal and temporal regions. These changes should be associated with functional change- the evidence reviewed suggests that frontal hypometabolism may be associated with motor slowing and disruption in executive tasks (Austin *et al*, 1992a; Moffoot *et al*, 1994; Elliott *et al*, 1996; Austin *et al*, 1992b; Curran *et al*, 1993; Dolan *et al*, 1994), such as planning, and that temporal changes may reflect general cognitive decline. The evidence also suggests that VBA is a valid method of analysing metabolic and perfusion data (Friston *et al*, 1995a; Friston *et al*, 1995b), allowing the localisation of functional changes in depression to be defined in a more spatially precise manner.

7.2 Striatal dopaminergic activity in depression

The primary question in the first experiment was if there was evidence of reduced striatal dopaminergic activity in those with depression. Using I^{123}-IBZM, a SPET ligand with high D2/3 receptor specificity and moderate affinity, there was evidence of increased specific uptake of the ligand at the right striatum in depressed patients, suggesting reduced endogenous dopamine release (Ebert *et al*, 1996; Shah *et al*,

1996; Ebert, 1998). Striatal IBZM uptake normally depends on both receptor density and competition with endogenous ligand. SPET imaging cannot allow absolute quantification of receptor density. Therefore, it is not possible to state unequivocally that increased uptake represents reduced endogenous dopamine release, but, several lines of evidence suggest that this is the correct interpretation of the findings. Further, increased binding (reduced endogenous dopamine release) correlated with objective measures of motor retardation, strengthening the evidence for a striato-frontal involvement in depression, the manifestation being motor retardation. This is consistant with functional, structural and neuropsychological studies suggesting a fronto-striatal deficit in depression.

7.3 Personality correlates of dopamine receptor availability

Although the effect size of the between group comparison was relatively large (about 0.8), the within-group variation in IBZM binding was unexplained. Both animal studies and indirect human studies suggest that the striatum may be involved in complex behaviours which may form the basis for temperament or personality. The dimension scores from three personality inventories were correlated with the specific striatal uptake ratios. Scores from Eysenck's psychoticism and neuroticism dimensions, and Cloninger's reward dependance dimension correlated in predicted directions with striatal IBZM uptake. Parallel PET and SPET data(Gray *et al*, 1994; Farde *et al*, 1997) also

provide supportive evidence that the normal variation in receptor density may be associated with variation in temperamental behaviours. Thus, dopamine receptor imaging may help identify the neurobiological substrate of personality traits and help elucidate the biological basis of temperament.

7.4 Functional vs structural striatal changes in depression

Because this first experiment was cross-sectional in design, it was not possible to state if the group differences represented state and/ or trait differences. On the one hand, SPET studies of striatal dopamine receptor availability before and after response to either medication (Ebert *et al*, 1996) or total sleep deprivation(Ebert, 1998) suggest a reversal of motor retardation and increased IBZM uptake. On the other hand, structural studies of patients with unipolar depression suggest fronto-striatal volume reductions (Soares & Mann, 1997). Longitudinal studies of combined structural and receptor imaging are required to examine if the substrate of striato-frontal volume reductions is reduced fronto-striatal dopaminergic neurones.

7.5 Review of structural brain changes in depression

What is the evidence that structural differences may be present in depressed patient? If so, are these differences acquired or predisposers to depression? The evidence related to these questions are reviewed in chapter 4. The review concludes that structural change is more evident

in the elderly with late onset (aged 60+) depression. The increasing effects of vascular disease with age may partially explain structural changes. These changes may be associated with treatment resistance and chronicity. It is suggested that temporal lobe change specifically may predispose to chronicity.

As hypercortisolism is frequently found in severe depression, one prediction is that depression should be associated with hippocampal atrophy, a structure known to be susceptible to the effects, amongst others, of cortisol. High resolution MRI techniques have already shown that patients recovered from recurrent depression exhibit reduced hippocampal volumes, suggesting just such a mechanism of neurotoxicity.. The review also concludes that fronto-striatal volume reductions have been the most consistant observations in patients with unipolar depression, particularly in the elderly and associated with motor slowing. Therefore, it would be predicted that CTRD, presumably associated with continuing hypercortisolism should exhibit hippocampal changes proportional to the total duration or severity of illness. Further, it may be expected that patients with CTRD would exhibit structural changes in fronto-striatal and temporal regions.

7.6 MRI changes in patients with CTRD

Do middle aged patients with CTRD and RD show structural changes, and if so, are they acquired, state dependant or markers of illness? These were the subject of the second experiment where high resolution brain MRI images were examined. Fronto-striatal atrophy was found in CTRD patients, using both SPM analysis (voxel based analysis) and conventional volumetry. Additionally, VBA revealed a combination of grey matter reductions and white matter increases in left hippocampus and rostral anterior cingulate regions, suggesting a change in the behaviour of water in these regions. Finally, there were extensive fronto-temporal grey density reductionds in the CTRD group, which appeared to be acquired, as they correlated with with measures of illness severity, such as the total number of ECT received. In contrast, hippocampal and rostral cingulate changes did not relate to total illness duration, present and previous severity, suggesting that these changes may be markers of chronicty or treatment resistance. The present results support the notion that rostral anterior cingulate hypoperfusion may be a marker of treatment resistance.

Both depressed groups showed reductions in medial prefrontal grey matter density (including Brodmann areas 9 and 10) with older age, an association not present in controls. Increasingly severe depressive symptoms and psychomotor retardation were both associated with reducing grey matter density in medial prefrontal cortex, particularly in Brodmann areas 9 and 10. In both patient groups, the degree of

clinical psychomotor slowing appeared to reflect the severity of preceding illness. This could indicate that, in a sample of middle aged patients, older patients may be more susceptible to prefrontal changes than younger patients or that older patients with melancholic depression suffer a fronto-striatal degeneration in proportion to the severity of the illness. It is tempting to speculate that melancholic depression associated with motor slowing may be associated with acquired, partially irreversible medial prefrontal grey matter reductions, accentuated by age, the degree of reduction dependant on age and severity.

7.7 Cognitive function in CTRD.

What is the pattern of cognitive deficits in patients with CTRD and RD, and do the deficits relate to structural change? These were the subject of chapter 6. Patients with CTRD were particularly impaired on episodic verbal memory and motor speed dependant task, but generally had a wide range of cognitive impairments,. General cognitive ability, as assessed by the NART, also showed deterioration in the CTRD group. The RD group exhibitedcontinued impairment in reaction time, but were otherwise unimpaired in other neuropsychological tasks. This residual slowing was unrelated to medication and paralleled clinically rated motor slowing.

Neuropsychological impairments were associated with grey density reductions in two areas. Psychomotor retardation and general cognitive ability

impairment both appeared to be related to frontal grey density reductions, particularly involving Broadman areas 9 and 10, but also inferomedial prefrontal cortex. Episodic verbal memory impairment related to reduced left hippocampal grey matter density. As the hippocampal grey matter was not related to any of the illness characteristics, it suggests that hippocampal structural change, together with memory impairment may represent a marker for chronicity and/or treatment resistance.

7.8 Psychomotor retardation in depression

The two experiments both suggest a central position for psychomotor retardation in the symptomatology of melancholic depression, as has been suggested by others (Widlöcher, 1983; Parker *et al*, 1993; Austin & Mitchell, 1995), and suggests that a frontostriatal correlate for motor slowing. It could be speculated that there is loss of striato-frontal dopaminergic neurones accounting for residual motor retardation on recovery and for striatofrontal atrophy in depression. This cannot be convincingly tested in cross-sectional studies such as the present ones.

7.9 Temporal lobe dysfunction and chronicity

The results also suggest that disrupted left temporal lobe integrity is associated with chronicity and treatment resistance. One limitation is that the studies have been cross-sectional. Therefore, it is not possible to rule out that these changes are state dependant. However, in

schizophrenia(Waddington, 1993) (O'Callaghan *et al*, 1995), obstetric complications may be linked to neurodevelopmental brain abnormalities, in particular left temporal lobe volume reduction and less pronounced cerebral lateralisation. Further, obstetric complications may be more frequent in patients with early onset depression or with bipolar disorder (Kinney *et al*, 1993) (Guth *et al*, 1993) (Done *et al*, 1991). It is, therefore, possible that neurodevelopmental abnormalities in patients with unipolar depression, particularly affecting the left temporal lobe, may predispose to chronicity.

Thus, it is not clear if the changes in the CTRD patients are, state dependant, related to the illness or its treatment, represent permanent anatomical differences or a combination of all these factors.

7.10 Validity of the voxel based analysis of structural MRIs.

Voxel based analysis of the MRIs produced results consistent with findings from previous functional and structural imaging studies. The results of VBA correctly predicted finding right fronto-striatal atrophy in patients with CTRD using volumetric analysis. However, VBA also revealed evidence of other MRI changes, probably representing local change in water content and not anatomical change, thus not detectable by conventional volumetry.

VBA is, therefore, a valid method of analysing "structural" images. VBA is operator independent, time efficient, unrestricted by a priori

hypotheses if necessary, and provides amore complete analysis of all aspects of the MRI data. VBA therefore promises to be a useful and efficient way of analysing MRIs in detail, particularly in psychiatric disorders.

7.11 Future directions

The challenge now is to characterise the natural history of the observed structural and functional brain changes in depression. If having a chronic illness leads to the development of structural changes, this will increase the pressure to treat depressed patients as quickly and effectively as possible. On the other hand, if these changes are antecedents of depression, it would be important to identify if they are related to birth trauma or abnormal neural developmental in utero. Ultimately, these findings support the idea that depression may appear clinically homogeneous, but severe refractory depression and late onset depression are indeed brain diseases.

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Appendix 3.1: Clinical data on 15 depressed and 15 control subjects undergoing imaging of D2/3 receptors using IBZM

Subject Number	AGE	SEX	Years full time education	Age of onset	Duration present episode (months)	Total number past episodes	Total number past admissions	Receiving psychotropic medication?	Receiving antidepressants?	Hamilton score (17-item)	Time post injection (minutes)	R striatal/ whole slice ratio	L striatal/ whole slice ratio	R striatal / frontal ratio	L striatal/ frontal ratio
D1	63	Female	9	58	8	3	3	yes	yes	16	131.38	1.74	1.69	1.91	1.89
D2	41	Male	18	24	6	2	0	yes	yes	22	115.67	1.73	1.69	1.87	1.83
D3	29	Female	14	19	16	1	1	yes	no	24	120.50	1.75	1.71	1.97	1.95
D4	63	Male	10	50	6	6	2	yes	yes	8	123.88	1.62	1.61	1.86	1.81
D5	47	Female	10	47	12	0	0	yes	no	26	125.38	1.64	1.65	1.81	1.83
D6	31	Male						yes	yes	22	130.00	1.75	1.73	1.97	1.95
D7	42	Male	12	38	10	2	1	no	no	24	114.50	1.77	1.73	2.05	2.05
D8	59	Female	10	34	16	2	2	yes	no	28	119.13	1.66	1.65	1.84	1.86
D9	30	Male	17	29	44	0	0	no	no	20	120.50	1.59	1.62	1.76	1.79
D10	61	Male	10	60	20	1	0	yes	yes	23					
D11	45	Male	17	22	8	1	1	no	no	28	115.75	1.55	1.55	1.72	1.73
D12	64	Female	9	63	3	0	0	yes	yes	42	116.00	1.74	1.69	1.99	1.94
D13	48	Male	13	39	4	3	1	no	no	31	140.50	1.55	1.48	1.60	1.53
D14	39	Male	17	20	4	1	0	yes	yes	17	112.63	1.78	1.78	2.18	2.18
D15	23	Female	11	20	4	1	0	yes	yes	21	111.08	1.70	1.65	1.91	1.84
C1	25	Male	16					no	no		121.31	1.64	1.51	1.83	1.69
C2	41	Female	11					no	no		121.50	1.55	1.50	1.64	1.61
C3	39	Male	20					no	no		118.29	1.55	1.57	1.73	1.76
C4	47	Male	15					no	no		124.02	1.66	1.61	1.77	1.73
C5	42	Female	14					no	no		122.25	1.65	1.74	1.91	2.01
C6	29	Male	14					no	no		117.33	1.52	1.57	1.67	1.71
C7	31	Female	14					no	no		122.38	1.67	1.72	1.80	1.85
C8	53	Male	14					no	no		124.88	1.59	1.59	1.82	1.82
C9	31	Female	13					no	no		120.25	1.67	1.74	1.77	1.80
C10	45	Female	18					no	no		106.54	1.78	1.73	1.96	1.89
C11	37	Male	15					no	no		113.83	1.57	1.59	1.75	1.78
C12	60	Male	17					no	no		108.88	1.53	1.52	1.68	1.65
C13	53	Male	15					no	no		114.33	1.58	1.68	1.68	1.77
C14	50	Male	15					no	no		119.38	1.66	1.66	1.79	1.77
C15	32	Female	16					no	no		121.29	1.69	1.71	1.95	1.96

Appendix 3.2: Individual scores on neuropsychological testing on 15 depressed and 15 healthy control subjects- part 1

Subject Number	AGE	SEX	NART derived IQ	Handedness score (-24 = left, +24= right dominant)	APSAQ score	BFS total score	BFS depressed mood score	BFS fatigue score	DSSR	DSS	AVLT total words	AVLT immediate recall B-list	AVLT A-list recall after B	AVLT delayed recall	AVLT delayed recognition
D1	63	Female	90	24	15	24	4	6			13	1	2	2	-9
D2	41	Male	120	24	4	42	14	10	66	13	57	8	14	14	14
D3	29	Female	118	19	4	5	0	0	65	12	65	4	14	15	15
D4	63	Male	117	24	9	37	8	6	51	12	42	6	6	6	10
D5	47	Female	103	24	11	39	12	2	45	9	27	3	5	3	11
D6	31	Male	115	16	20	40	10	14	53	9	62	9	15	15	14
D7	42	Male	121	23	2	30	8	0	61	11	56	7	11	11	14
D8	59	Female	103	22	5	29	2	10	43	10	50	6	12	12	11
D9	30	Male	124	23	1	2	0	2	60	11	65	6	15	15	15
D10	61	Male	106	23	4	11	0	2	37	9	33	3	7	6	13
D11	45	Male	113	22	0				52	11	49	5	10	9	12
D12	64	Female													
D13	48	Male	116	24	22	32	6	8	30	6	50	7	11	10	15
D14	39	Male	117	18	2	7	0	4	43	8	43	7	10	10	13
D15	23	Female	105	23	19	27	8	10	65		57	4	11	13	15
C1	25	Male	121	16	13	6	6	0	48	8	53	6	10	8	11
C2	41	Female	100	24	6	11	4	0	57	11	48	6	10	9	11
C3	39	Male	116	13	7	4	0	0	54	10	52	5	13	14	15
C4	47	Male	123	-2	6	15	0	4	52	11	45	3	13	10	14
C5	42	Female	112	24	1	3	0	0	71	14	56	6	13	14	14
C6	29	Male				24	6	6							
C7	31	Female	110	24	4	2	2	0	62	11	52	7	13	13	15
C8	53	Male	120	24	1	4	2	0	55	12	45	6	11	8	14
C9	31	Female	107	23	2	9	0	2	71	13	68	8	10	11	12
C10	45	Female	118	20	9	13	0	8	52	12	67	7	15	15	15
C11	37	Male	15	22	0	27	0	2	52	10	50	6	14	14	15
C12	60	Male	123	18	1	1	0	0	52	12	55	14	10	13	13
C13	53	Male	5	22	2	4	2	0	51	11	56	13	9	14	14
C14	50	Male	122	20	5	4	0	0	48	10	50	6	7	5	5
C15	32	Female	121	2	7	6	0	4			67	8	14	15	15

Appendix 3.3: Individual scores on neuropsychological testing on 15 depressed and 15 healthy control subjects- part 2

Subject Number	AGE	SEX	Verbal fluency total (No. of words in 3 mins)	Trails-A (seconds)	Trails- B (seconds)	Reaction time "thinking" time (msec)	Reaction time "movement" time (msec)	Reaction time total time (msec)	Maximal voluntary contraction (kg)
D1	63	Female	4			1036	1596	1366	12
D2	41	Male	42	32	52	475	317	595	59
D3	29	Female	64	34	60	407	545	605	29.3
D4	63	Male	36	27	56	424	248	518	51.3
D5	47	Female	30	35	104	558	381	696	21
D6	31	Male	40	27	45	401	322	520	37
D7	42	Male	20	30	49	467	419	610	38.2
D8	59	Female	31	46	427	635	438	805	22.6
D9	30	Male	68	41	52	423	309	537	54
D10	61	Male	48	52	85	544	496	736	20.5
D11	45	Male	64	21	35	465	363	595	18.6
D12	64	Female							
D13	48	Male	55	33	95	503	319	619	23.3
D14	39	Male	16	28	59	566	705	827	48.6
D15	23	Female	43	28	45	456	381	594	22
C1	25	Male	33	37	51	441	316	551	44
C2	41	Female	39	49	77	423	290	530	27
C3	39	Male	62	31	36	435	284	532	57
C4	47	Male	47	32	77	486	389	627	65.1
C5	42	Female	44	29	30	446	346	580	33
C6	29	Male							48
C7	31	Female	47	42	69	459	318	577	36
C8	53	Male	55	22	38	507	391	652	69
C9	31	Female	48	22	34	360	313	480	29.3
C10	45	Female	64	31	62	404	340	530	29.6
C11	37	Male	32	23	62	473	419	632	52
C12	60	Male	49	29	68	442	238	531	44.6
C13	53	Male	60	34	39	463	363	595	58
C14	50	Male	50	42	68	546	392	688	53.6
C15	32	Female	46	21	44	396	227	482	31.3

Appendix 5.1: Individual clinical and medication data on twenty patients with CTRD and 20 with RD.

Patient ID (D= CTRD, R= RD group)	Sex	Total illness duration (weeks)	Total no. episodes	No. of hospital admissions	Total no. ECT	Number of adquate trials of class of antidepressant						No. of times previously prescribed neuroleptics
						Tricyclics	SSRIs	MAOIs	Lithium	ECT	Other antidepressants*	
D1	Female	308	4	10	25	8	3			3		5
D2	Female	425	5	4	15	9	3	2	2	2	1	4
D3	Male	225	1	4	7	3	7	2	1	3	2	3
D4	Male	538	2	1	14	3	1			1		
D5	Female	746	7	23	133	6	4	2	3	3	3	6
D6	Male	144	1	2	22	3	1		1	2	1	
D7	Female	234	3	0	0	3	2	1			2	1
D8	Male	399	1	8	50	3			1	5	2	2
D9	Male	264	3	1	0	3	2		1			
D10	Male	160	1	0	0	1	1	1			1	
D11	Male	507	1	0	0	2	1	2				1
D12	Male	130	1	2	13	4	1		2	2	1	2
D13	Male	108	1	2	5	2	1		1	1	2	2
D14	Female	130	1	2	8	3	1	1	1	1	1	4
D15	Female	247	4	5	17	4	3	2	2	3	1	2
D16	Male	217	3	0	3	3	1	1		1	2	1
D17	Female	425	4	5	16	3	1	1	1	5	1	4
D18	Male	173	3	2	0	1		1			1	2
D19	Male	208	1	5	8	2	1	1	1		1	2
D20	Male	152	1	0	0	2	1					1

*Other antidepressants included, Trazodone, venlafaxine, and mianserin.

Adequecy of dose was judged according to BNF guidelines.

Appendix 5.1: Individual clinical and medication data on twenty patients with CTRD and 20 with RD.

Patient ID (D= CTRD, R= RD group)	Sex	Total illness duration (weeks)	Total no. episodes	No. of hospital admissions	Total no. ECT	Number of adquate trials of class of antidepressant						No. of times previously prescribed neuroleptics
						Tricyclics	SSRIs	MAOIs	Lithium	ECT	Other antidepressants*	
R1	Male	54	2	2	0	1				2		2
R2	Male	65	2	3	7	1						1
R3	Female	214	5	0	0	4	1					1
R4	Male	173	8	5	0	3		1	1	3		2
R5	Male	186	5	2	6	2			1	1		
R6	Male	52	2	1	5		2					
R7	Male	6	2	1	5	3						1
R8	Female	56	3	1	5	2						
R9	Male	26	1	1	5	1	1					1
R10	Male	18	1	1	5	1	2					
R11	Female	31	1	1	8	1				1		
R12	Male	52	1	1	7					1	1	
R13	Female	130	5	2	3	4	1			2		
R14	Male	91	3	1	0	2						
R15	Male	87	2	0	0	1	1					
R16	Female	35	1	1	0	1	1					
R17	Male	52	2	0	0	3	1				1	
R18	Female	100	2	2	0	2					2	
R19	Female	36	1	0	0		1					
R20	Male	54	1	1	8	2	1					

*Other antidepressants included, Trazodone, venlafaxine, and mianserin.

Adequecy of dose was judged according to BNF guidelines.

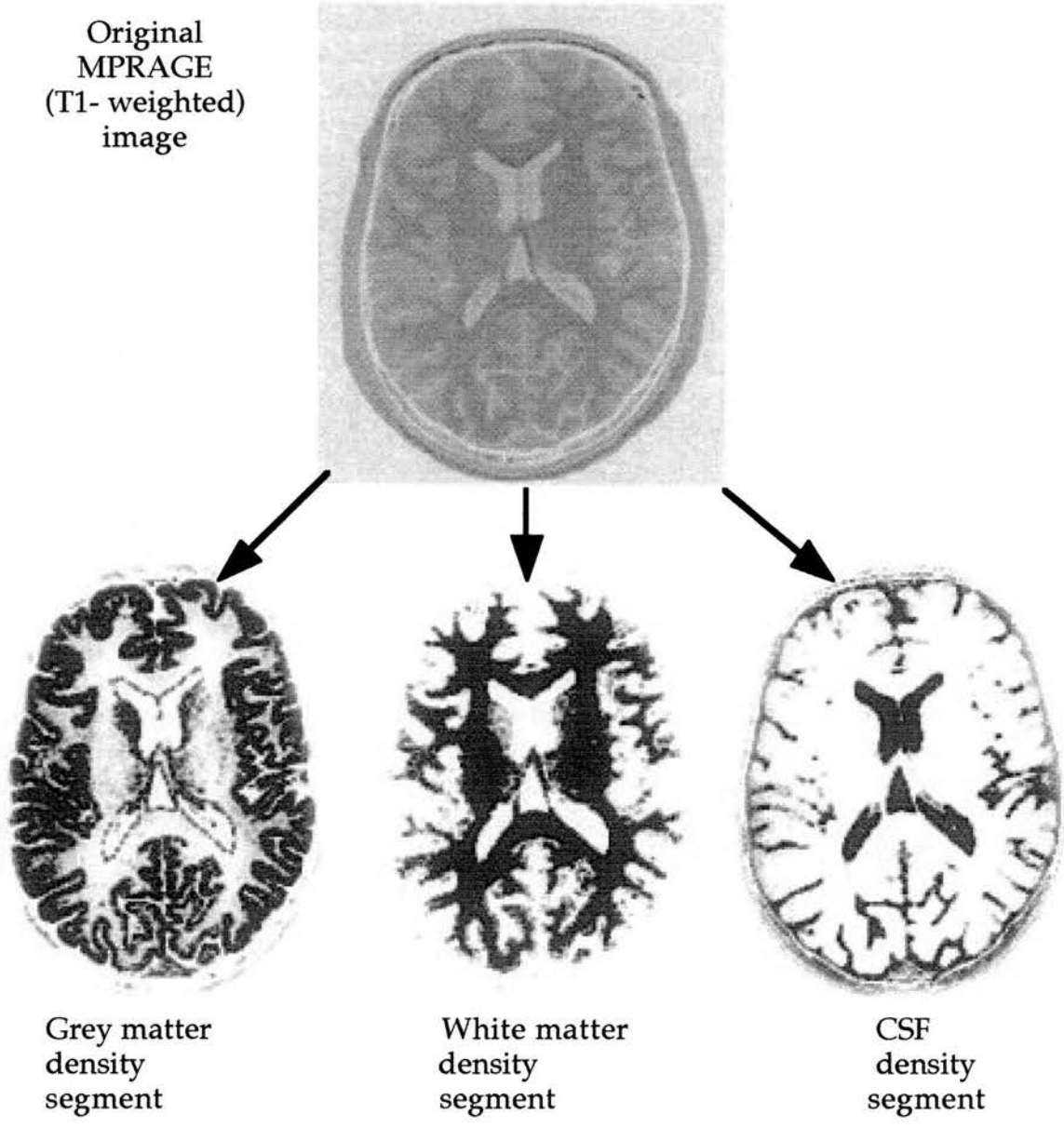
Appendix 5.2: Individual data on features of the depressive illness in 20 patients with CTRD and 20 with RD.

Patient ID	Total no. episodes	Age	Age at onset of first episode	Age at onset of last episode	Duration of current episode (weeks)	Longest episode duration (weeks)	Total duration hospitalisation (weeks)	Total illness duration (weeks)	No. of hospital admissions	Total no. ECT
D1	4	27	19	24	130	130	180	308	10	25
D2	5	41	25	37	108	108	63	425	4	15
D3	1	46	50	50	104	104	59	225	4	7
D4	2	57	37	40	486	486	2	538	1	14
D5	7	45	27	41	160	160	123	746	23	133
D6	1	50	49	49	144	144	14	144	2	22
D7	3	55	41	53	108	108	0	234	0	0
D8	1	54	48	48	399	399	40	399	8	50
D9	3	43	34	39	212	212	2	264	1	0
D10	1	49	47	47	160	160	0	160	0	0
D11	1	54	45	45	507	507	0	507	0	0
D12	1	64	61	61	130	130	23	130	2	13
D13	1	62	60	60	108	108	38	108	2	5
D14	1	43	43	43	130	130	23	130	2	8
D15	4	40	18	40	104	208	44	247	5	17
D16	3	58	29	55	178	178	0	217	0	3
D17	4	41	23	37	173	173	16	425	5	16
D18	3	59	24	58	113	113	1	173	2	0
D19	1	57	54	54	208	208	13	208	5	8
D20	1	33	30	30	152	152	0	152	0	0

Appendix 5.2: Individual data on features of the depressive illness in 20 patients with CTRD and 20 with RD.

Patient ID	Total no. episodes	Age	Age at onset of first episode	Age at onset of last episode	Duration of current episode (weeks)	Longest episode duration (weeks)	Total duration hospitalisation (weeks)	Total illness duration (weeks)	No. of hospital admissions	Total no. ECT
R1	2	34	44	45		18	54	54	2	0
R2	2	47	29	31		39	65	65	3	7
R3	5	44	25	40		182	214	214	0	0
R4	8	49	40	50		65	173	173	5	0
R5	5	65	22	60		48	186	186	2	6
R6	2	62	41	57		36	52	52	1	5
R7	2	62	42	45		4	6	6	1	5
R8	3	45	56	62		74	56	56	1	5
R9	1	53	49	49		26	26	26	1	5
R10	1	49	47	47		18	18	18	1	5
R11	1	48	46	46		31	31	31	1	8
R12	1	52	47	47		52	52	52	1	7
R13	5	51	30	48		39	130	130	2	3
R14	3	43	37	42		42	91	91	1	0
R15	2	52	39	48		52	87	87	0	0
R16	1	39	33	33		35	35	35	1	0
R17	2	31	22	28		31	52	52	0	0
R18	2	40	36	38		69	100	100	2	0
R19	1	30	27	27		36		36	0	0
R20	1	59	53	53		31		54	1	8

Appendix 5.3- An example of the results from the automated segmentation of an MPRAGE MRI image by SPM '96.



(Darker areas represent higher density of the tissue examined)

APPENDIX 5.4: Volumetric analysis

1. Preparation of MR images

The MR images were analysed using the ANALYSE program running on a Unix-based Sun workstation (Sun Microsystems). Images were initially converted to 8-bit images. Non- brain tissue such as meninges, skull and scalp were removed by ascertaining the threshold voxel intensity between grey matter and CSF. Tissue below this threshold (surrounding CSF) and exterior to this rim of CSF (skull, scalp and meninges) were excluded. Where meningeal tissue abutted on cerebral tissue, this was manually removed using an anatomical atlas as a guide.

Although the images were, as far as possible, acquired perpendicular to the AC-PC line, visual inspection confirmed that some images had small amounts of tilt (rotation around the x-axis), roll (rotation around the y-axis) and/or yaw (rotation around the z-axis). All images were re-orientated correcting for these. A one-bit template was produced for each image, and both this template and the original image were resliced in the correct orientation in Analyse. Trilinear interpolation was used for the original image, but nearest neighbour interpolation was used for the one-bit template. This ensured that partial volume effects would not be introduced at the exterior edges of cerebral tissue in the one bit template. After reorientation, the original image and 1-bit

template image were multiplied, thus removing extra volume added to the original image as a result of partial voluming at the exterior edge of cerebral tissue. The total cerebral volume thus remained unchanged after re-orientation.

2. Landmarks used to delineate the structures.

A number of studies were reviewed (Appendix 5.4(1)- Appendix 5.4(2)) examining landmarks that other researchers have previously used to delineate structures. On the basis of this, the criteria in Appendix 5.4(3) were devised. The hippocampus was divided into anterior and posterior portions, using the presence of the mamillary bodies as a landmark. No attempt was made to measure amygdala volume separately. The caudate and putamen were measured bilaterally, as well as prefrontal tissue (frontal tissue anterior to the genu of the corpus callosum), "posterior frontal" tissue (frontal tissue between the anterior edge of the genu of the corpus callosum and the slice in which the anterior commisure presented most medially and horizontally), and the temporal lobes.

3. Segmentation of MRIs.

Two investigators underwent training to accurately identify landmarks and to reliably segment images into the areas mentioned above. MR images were then anonymised by a third investigator. Half

the images from each subject group were randomly chosen to be flipped so that left and right sides were reversed. The two investigators who segmented the MR images were thus blind to the left-right orientation and diagnostic group membership of the images. Five random images were chosen to be analysed by both investigators independently, allowing a measurement of inter-rater reliability. One of the investigators performed a repeat analysis of the same five images two months later, producing a measure of intra-rater reliability. These measurements are shown in Appendix 5.4(4).

The two investigators each independently analysed the images from half the total subjects.

4. Statistical analysis

The results of preceding voxel based analysis predicted volume reductions particularly in the right prefrontal and basal ganglia regions. VBA also indicated smaller reductions in left prefrontal and basal ganglia regions. The greatest differences were comparing controls with the CTRD group. Thus, one-tailed t-tests were used (SPSS for the MacIntosh v4.0), as the direction of change was predicted, and no correction for multiple comparisons was used, as there were specific hypotheses about the regions showing volumetric reductions. As the total cerebral tissue volume did not differ

between the three groups (Appendix 5.4(5b)), controlling for total volume in the group comparison was not required.

5. Result

As predicted, the CTRD group had reduced right caudate and right prefrontal tissue volumes compared to controls (Appendix 5.4(5a and 5b)). In comparison to recovered patients, the CTRD group had bilateral caudate volume reductions, but no change in prefrontal volume. As predicted by VBA analysis, there were no other volume changes in any other region. These results effectively validate the findings of right fronto-striatal atrophy found using VBA.

Appendix5.4(1): Selected review of landmarks used in segmenting anatomical structures in the brain -part 1

Reference	Frontal lobe	Temporal lobe	amygdala/ hippocampus	deep gray matter	Rater reliability
Coffey et al, 1993	All slices anterior to and including optic chiasm	Posterior limit= level of colliculi. supero-medial= line joining lateral ventricle to sylvian fissure either at inferior most part or medial most part. Line drawn perpendicular to axis of temporal stem	Posterior limit= slice with interpeduncular cistern. Measured areas in this and next three slices.		interrater reliability corr= 0.88 to 0.99. Intrarater reliability corr= 0.93 to 0.99
Axelson et al. 1993			"systematic sampling". Anterior limit= "first sect. with amygdala. Posterior limit= where gyrus fasciiolaris and upward curving of fibriae were noted.		Intra class corr bet. raters= 0.86/ 0.90
Aylward et al 1994				caudate; inferior= immediately superior to the crossing of the anterior commisure over midline. Medial= lateral ventricle Lat= ant limb internal cap, post border of thalamus, vent striae	Intrarater= 0.99, Interrater>0.9
Sheline et al., 1996			Posterior limit= hippocampus first appearing adjacent to trigone of 3rd ventricle, Anterior limit= white matter border between amygdala and hippocampus or a line connecting the sulcus semiannularis and inf horn lat vent.		Intrarater corr coef= 0.89 to 0.96 Interrater cc= 0.94 to 0.95
Suddath et al 1989; Suddath et al 1990	Prefrontal= anterior to genu of corpus callosum	Posterior limit= last section in which Sylvian fissure identified. Medially= line from most inf aspect of Sylvian fiss to temp horn of lat vent OR line from most medial aspect of Sylvian fiss to temp horn of lat vent, both perpendic to stem of temp lobe.	No clear guidelines. Based on 6 contiguous slices through correct region. Amygdala assumed to be present in slice 1, hippocampus slice 2 to 4. Indistinct boundaries assessed by reference to an atlas	not measured	Interrater= 0.92- 0.98
Weinberger et al 1992	not measured		Pes hippocampus= first 4 slices posterior to amygdala including slice through the amygdala-hippocampal junction.		Unknown

Reference	Frontal lobe	Temporal lobe	amygdala/ hippocampus	deep gray matter	Rater reliability
Bogerts et al.1990	not measured.	Posterior= where the ascending crus fornix surrounding the pulvinar is interrupted in coronal section.	Divided into anterior and posterior portions. Posterior portion; posterior limit= as for temporal lobe. Anterior limit= first slice with mammillary bodies. Anterior portion; post limit= first slice ant. to mam body. Ant limit= where amyg. lost oval shape.	Not measured	Interrater and test-retest correlation= 0.85 to 0.93
DeLisi et al.1991	Posterior= section showing optic chiasm and sella turcica Mean=163.35 (28.8)	Posterior limit= sections showing auditory canal. Medial= straight line from medial tip of lower limb of sylvian fissure to point where temporal and frontal lobes seperate medially.	"In all slices where structures could be seen clearly"	On axial images, dependent on natural boundaries of caudate and lentiform.	Intraclass corr.= 0.90 to 0.99
Shenton et al. 1992	Superior frontal gyrus; anterior= naturalistic. posterior= first slice with complete crossing of anterior commisure fibres	a. sup. temp. gyrus (stg)= as for ant. and post hipp. b. temp lobe= as for stg c. ant pole; ant= 2nd slice showing temp lobe. post= slice immediately ant. to beginnning of stg and amygdala	Ant. portion; ant= WM tract linking temporal lobe to rest of brain. post= last slice before mam bods. Post. portion; Ant.= first with mamillary bodiess. posterior= last appearance of crus fornix.	not measured	Average intraclass correlation= 0.86
		supero-med boundary= from sylvian point, diagonal line to uppermost part of amyghipp complex and then medially to lat. ventricle or along the complex.			
Desmond et al 1994		not measured	Anterior= pit stalk. Posterior= pulvinar. Amygdala= slices 1-2. ant hippocampus= 2- 4, post hipp= 5-7		volumes varied 3- 9%
Bremner et al 1995		Post limit= slice before superior colliculus.	Post limit= slice before superior colliculus. Measured the 5 contig. slices (15mm) from this slice.	Caudate; ant. limit= first slice with genu corpus callosum and ant. horns lat. ventricle, post. limit= section before trigone of lat ventricle and splenium of corpus callosum.	Interrater reliability. coeff= 0.76 0.78 Intrarater reliability coeff= 0.7- 0.78

Appendix 5.4(3): Landmarks used to define boundaries of anatomical structures in the brain

Region	Anterior boundary	Posterior boundary	Medial boundary
"Prefrontal lobe"	Naturalistic	Slice anterior to the genu of the corpus callosum	
"Posterior frontal lobe"	First slice with genu of corpus callosum	Slice with most medial presentation (horizontal at midline) of anterior commisure	
Temporal lobe	Naturalistic	The most posterior slice containing distinct bundles of the crus fornix	From most inferior or medial tip of Sylvian fissure, a diagonal line to uppermost part of amygdala-hippocampal complex and then medially to the lateral ventricle or along the complex.
Cerebellum	Naturalistic	Naturalistic	
Caudate	Naturalistic	Last slice with mammilary bodies	
Putamen	Naturalistic	Last slice with mammilary bodies. Pallidus was included up to one in which columns of fornix were prominent	
Anterior hippocampus	Naturalistic, including amygdala	Last slice with mammilary bodies	
Posterior hippocampus	First slice posterior to mamillary bodies	The most posterior slice containing distinct bundles of the crus fornix	

Appendix 5.4(4): Inter- and intra-rater reliability coefficients for volume measurements.

Area	Inter-rater reliability coefficient	Intra-rater reliability coefficient
R. Anterior Hippocampus	0.85	0.85
L. Anterior Hippocampus	0.87	0.76
R posterior hippocampus	0.99	0.97
L posterior hippocampus	0.91	0.88
R total hippocampus	0.92	0.93
L total hippocampus	0.92	0.91
R Caudate	0.93	0.99
L Caudate	0.93	0.87
R putamen	0.96	0.98
L putamen	0.9	0.98
R prefrontal	0.99	0.98
L prefrontal	0.99	0.98
R Posterior prefrontal	0.99	0.98
L Posterior prefrontal	0.99	0.97
R temporal lobe	0.93	0.93
L temporal lobe	0.98	0.97
R cerebellum	0.91	0.94
L cerebellum	0.96	0.91

Appendix 5.4(5a): Volume measurements between three subject groups- part 1.

Region	Volume (mm^3)- SD in parentheses			Chronic vs controls			Chronic vs recovereds		
	Chronic group	Controls	Recovered group	t-value	probability (1-tailed)	effect size	t-value	probability (1-tailed)	effect size
R. anterior hippocampus	1822 (566)	1829 (564)	1807 (452)	-0.04	0.48	0.01	0.09	0.46	-0.03
L. anterior hippocampus	1529 (450)	1663 (561)	1728 (488)	-0.83	0.2	0.26	-1.35	0.09	0.42
R. Posterior hippocampus	3582 (641)	3566 (413)	3791 (637)	0.09	0.46	-0.03	-1.03	0.15	0.33
L. Posterior hippocampus	3722 (593)	3623 (467)	3848 (555)	0.58	0.28	-0.19	-0.69	0.24	0.22
R. hippocampus	5405 (795)	5396 (592)	5599 (743)	0.04	0.48	-0.01	-0.8	0.21	0.25
L. hippocampus	5250 (712)	5286 (636)	5576 (722)	-0.17	0.43	0.05	-1.44	0.08	0.45
R. caudate	3505 (472)	3766 (499)	3796 (563)	**-1.7**	**0.048**	**0.54**	**-1.77**	**0.04**	**0.56**
L. caudate	3500 (428)	3645 (488)	3795 (537)	-1	0.16	0.32	**-1.92**	**0.03**	**0.61**
R. putamen	4471 (747)	4670 (575)	4509 (574)	-0.95	0.17	0.30	-0.18	0.42	0.06
L. putamen	4366 (505)	4483 (632)	4408 (549)	-0.65	0.26	0.21	-0.26	0.4	0.08

Appendix 5.4(5b): Volume measurements between three subject groups- part 2.

Region	Volume (mm^3)- SD in parentheses			Chronic vs controls			Chronic vs recovereds		
	Chronic group	Controls	Recovered group	t-value	probability (1-tailed)	effect size	t-value	probability (1-tailed)	effect size
R. prefrontal lobe	65184 (7676)	71170 (8477)	68575 (11077)	**-2.34**	**0.012**	**0.74**	-1.13	0.13	0.36
L. prefrontal lobe	63265 (6603)	66421 (8948)	65623 (8401)	-1.27	0.1	0.41	-0.99	0.16	0.31
R. posterior frontal lobe	93551 (10929)	95734 (9956)	97755 (12983)	-0.66	0.25	0.21	-1.11	0.23	0.35
L. posterior frontal lobe	92647 (10508)	93900 (11128)	96921 (11657)	-0.37	0.35	0.12	-1.22	0.11	0.39
R. temporal lobe	76688 (7580)	80087 (8523)	79850 (9573)	-1.33	0.08	0.42	-1.16	0.12	0.37
L. temporal lobe	74476 (7238)	76478 (7742)	78227 (8494)	-0.84	0.2	0.27	-1.5	0.07	0.48
R. cerebellum	69219 (6866)	72577 (7678)	71798 (8023)	-1.46	0.07	0.46	-1.09	0.14	0.35
L. cerebellum	69095 (6229)	72668 (7716)	71622 (7233)	-1.61	0.058	0.51	-1.18	0.12	0.38
Total volume	1305950 (128281)	1307750 (96960)	1307500 (125870)	-0.05	0.48	0.02	-0.04	0.48	0.02

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Clinical and psychometric correlates of dopamine D_2 binding in depression

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ABSTRACT

Background. Single photon emission tomography (SPET) with the dopamine $D_{2/3}$ ligand ^{123}I-IBZM gives a semi-quantitative estimate of dopamine binding. In depressed patients, we predicted evidence of reduced function, i.e. increased binding, particularly in more retarded patients.

Methods. Fifteen depressed patients with major depressive illness and 15 healthy, age- and sex-matched volunteers were examined with a clinical and neuropsychological test battery and high resolution IBZM-SPET. Estimates for specific binding were computed by averaging striatum to whole slice or frontal uptake ratios over 8–10 scans acquired from 70 min after tracer injection.

Results. Using whole slice as reference, left striatal uptake ratios did not significantly differ for patients from controls. Right ratios were significantly higher in patients than controls ($P = 0{\cdot}03$). There were significant correlations between IBZM binding in left and right striatum and measures of reaction time and verbal fluency.

Conclusions. Increased IBZM binding in striatum probably reflects reduced dopamine function, whether due to reduced release of dopamine, or secondary up-regulation of receptors. The observed abnormalities may be trait or state related, an issue that needs to be addressed with longitudinal study designs. The possible role of medication as a confounding variable requires further exploration.

INTRODUCTION

The role of serotonergic and noradrenergic neurotransmitter systems in the pathogenesis of depression is widely accepted, but several lines of evidence also point to an involvement of dopaminergic mechanisms. First, a reduced turnover of dopamine, determined by the measurement of homovanillic acid in cerebrospinal fluid, has been demonstrated in depressed patients, particularly if motor retardation is present (van Praag & Korf, 1975; Jimerson, 1987). Secondly, many antidepressants, such as tricyclics, monoamine oxidase inhibitors, nomifensine, bupropion and electro-convulsive treatment, exhibit direct or indirect dopamine enhancing effects. Moreover, some agents with mainly dopaminergic effects, amphetamine, pirebidil and bromocriptine, may have antidepressant action (Diehl & Gershon, 1992). Thirdly, the mesolimbic dopaminergic system with its projections to medial frontal cortex has been implicated in depressive behaviour in humans and in animal models of reward-seeking behaviour (Fibiger, 1993). In the human brain, the anterior cingulate is densely innervated by dopaminergic neurones. Parkinson's disease is associated both with (anterior cingulate) dopaminergic depletion and a high rate of depression (Cummings, 1992). Finally, studies of cerebral perfusion have implicated the cingulate gyrus, the fronto-orbital cortex and basal ganglia in the recovery from depression after pharmacotherapy (Goodwin *et al.* 1993) and ECT (Lerer *et al.* 1994; Scott *et al.* 1994).

Three single photon emission tomography (SPET) studies have examined dopamine function more directly in depression, by using ^{123}I-IBZM (^{123}I-3-iodo-methoxybenzamide), a benzamide derivative with high $D_{2/3}$ receptor sel-

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ectivity (Verhoeff *et al.* 1992), but moderate affinity to dopamine receptors. Its specific binding, therefore, reflects receptor binding and any partial displacement by endogenous ligand (Laruelle *et al.* 1995). Specific IBZM binding in the striatal regions of interest (ROIs) was increased in the depressed group compared with controls, suggesting either a reduction in the competition from endogenous dopamine or an up-regulation or increased affinity to IBZM of $D_{2/3}$ receptors (D'haenen & Bossuyt, 1994). A second study could not statistically confirm this group difference for the depressed patients examined, but found IBZM binding to be specifically higher in patients with clinically rated psychomotor retardation (Ebert *et al.* 1996). IBZM binding was reduced after successful pharmacological treatment and a concomitant improvement in motor retardation (Ebert *et al.* 1996). The same pattern of change in IBZM binding was found in depressed patients with a successful antidepressant response to total sleep deprivation (Ebert *et al.* 1994).

Ebert *et al.* (1996) dichotomized patients by the presence or absence of retardation, but they did not specifically investigate the cross-sectional relationship between IBZM binding in depression and more objective measures of speed, reflecting motor and cognitive components of retardation. We designed this study to compare IBZM binding in the basal ganglia in a depressed group with matched healthy volunteers, predicting a significant excess of binding in the patients, which was likely to be correlated with objective measures of motor and cognitive speed.

METHOD

Subjects

The design of the study was approved by the local research ethics committee and the appropriate committee at the Department of Health (ARSAC). Written informed consent was obtained from all participating subjects. Fifteen in-patients (nine males and six females) from the Royal Edinburgh Hospital who fulfilled DSM-III-R criteria (American Psychiatric Association, 1987) for a current major depressive episode with or without melancholic or mood-congruent psychotic features and 15 healthy volunteers were entered into the study. The groups were matched for age, sex, and premorbid IQ.

Two of the depressed patients had a bipolar affective disorder. Eight patients were on antidepressant medication (including lithium) only, three were on benzodiazepines only. The remaining four were free of all medication at the time of scanning. For at least 3 months prior to the investigation, patients had not received any medication that acted directly on the dopamine system, such as neuroleptics. The severity of symptoms was assessed using the 17-item Hamilton Depression Rating Scale (Hamilton, 1960) and the patient's position on the neurotic/endogenous continuum was measured by the Newcastle scale (Carney *et al.* 1965).

Controls were screened for the presence of psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978) and they were free of any medication. Both patients and controls were required to be in good physical health, particularly with no evidence of alcohol or substance misuse, significant neurological illnesses or brain trauma. All patients were right-handed, two of the controls were predominantly left-handed.

Imaging protocol

Subjects were imaged with a 12 detector, brain dedicated SPET camera, with an in-slice and *z*-axis resolution of approximately 8·5 mm (full width half maximum), and a sensitivity of 520 cps in a head-sized phantom filled with 1 kBq/ml (Ebmeier *et al.* 1991).

All subjects took oral doses of potassium iodate to ensure thyroid saturation with iodine and to prevent its excess exposure to radiation, 170 mg each on the night before and the morning of the scan, 85 mg after the scan. All scans were performed in the morning. An in-dwelling catheter was inserted into an arm vein 15–30 min before the injection of 185 MBq of ^{123}I-IBZM over a period of 30 s. During and for 5 min after injection, patients were required to lie still and silent wearing eye patches with ears unplugged, with background noise kept to a minimum. The subject's head was then placed in a moulded headrest, positioned with the help of two crossed light beams, and fixed with two pressure pads over the zygomatic arches.

Slices were acquired parallel to the orbitomeatal line (OML). During the first hour, a full

scan of the brain was carried out, followed by a short sequence of scans around the level of the basal ganglia, allowing the operator to choose the slice position with maximum activity from the striatum, approximately 4 cm above the OML. Single slices were then acquired at this level in a time series from 80 min to 140 min post-injection. IBZM studies in healthy volunteers have found specific activity to be at a steady state during this period (Verhoeff *et al.* 1992).

Analyses of the scans were carried out by a physics technician who was blind to the clinical details. Regions of interest (ROIs) were drawn in advance from the transaxial slice at the level of the anterior and posterior commissure taken from a standard brain atlas (Talairach *et al.* 1988), outlining left and right frontal cortex, striata and brain slice hemispheres. The complete templates were linearly re-positioned, re-sized and deformed, so that the outlines of the hemisphere ROIs fit over the cortical rim, as defined by the 20% isocontour line of the scan (Ebmeier *et al.* 1991). The striatal ROIs were then re-positioned and centred over the maximum striatal activity by hand if necessary, but were not further re-sized. Once the template position had been determined for each subject for the first scan, no further adjustment of the template was permitted. Following the previous studies, a regional uptake ratio was calculated as the ratio of the striatal ROI activity to reference ROI. With this approach, striatal activity (presumed to represent specific + non-specific binding + free ligand) is compared to a background region (non-specific binding + free ligand), providing a functional index of specific binding of IBZM to $D_{2/3}$ receptors. The choice of the reference region may affect results, particularly if it includes the basal ganglia. For example, the use of whole slice ratios may reduce the power of comparisons by including areas with high specific binding in both numerator and denominator (Ebert *et al.* 1996). On the other hand, using a smaller reference region may increase the variability of the uptake ratios (Ebmeier *et al.* 1991). Finally, it has to be considered that non-specific binding may not be the same for different subjects and thus may confound group comparisons (Laruelle *et al.* 1995). For comparison purposes, we chose two reference regions – whole slice and frontal cortex. Regional uptake ratios were calculated for each scan in the time series and were then averaged across 8–10 scans to remove noise. The mean time of the scans was well matched for the two groups (118 (S.D. = 5) min in controls *v.* 121 (S.D. = 8) min in patients post-injection).

Neuropsychological testing

All subjects were tested under standardized conditions. On the morning prior to the scan subjects performed the National Adult Reading Test revised (Nelson & Willison, 1991) to measure pre-morbid IQ, the auditory verbal learning test (AVLT; Rey, 1964; Lezak, 1983), the Digit Symbol Substitution Test (DSST; Wechsler, 1981), Trail-making A and B from the Army Individual Test Battery (Army Individual Test Battery, 1944), the FAS-Verbal Fluency test (Borkowski *et al.* 1967) and the reaction time tasks from the CANTAB computerized psychometric testing battery (Sahakian & Owen, 1992), which allow for a separate determination of the response initiation and movement times.

On the morning of the scan, subjects performed a maximum voluntary contraction (MVC) task. Each subject was asked to squeeze a dynamometer as hard as they could, and the average of three trials with the right hand was used for analysis. This follows the work of Cohen *et al.* (1982) who demonstrated that deficits in motor performance in depressed patients was proportionate to their level of depression and also Moffoot *et al.* (1994) who found a reduction in performance in melancholically depressed patients sensitive to diurnal variations in mood. It has been suggested that a reduced performance may reflect a generalized reduction in central motivational state or in effort. Subjects also completed the Befindlichskeitskala (BFS; von Zerssen *et al.* 1974), an adjective check list of 28 word-pairs reflecting their present state of mind. The scale has two subscores, one for the degree of fatigue experienced, the other for the degree of depression felt. Finally, the Alderly Park State Anxiety Questionnaire (APSAQ; Walker, 1990) was used to assess the subject's level of state anxiety just after the injection of the ligand.

A subgroup of the healthy volunteers completed the Eysenck Personality Questionnaire to determine extraversion, neuroticism and psychoticism (Eysenck & Eysenck, 1975).

Statistics

Data were analysed with SPSS (version 4) for the Apple Macintosh. Since clear hypotheses existed for the direction of group differences, comparisons were made by one-tailed Mann–Whitney *U* tests. For correlations between Hamilton scores, psychometric tests and striatal tracer uptake, Spearman's one-tailed correlation coefficients were computed. Non-parametric tests were used consistently, because some variables were not normally distributed. Exploratory correlations are descriptive, or at best hypothesis generating. Univariate 95% confidence intervals (CI) were computed for the correlation coefficients to provide a more practical description of the effect. However, correlations of measures of psychomotor retardation with striatal IBZM uptake were planned, hypothesis testing, and therefore do not require correction for multiple comparisons.

RESULTS

As Table 1 shows, patients and controls were well matched for age and sex. There was a trend for depressed patients to have fewer years of education than controls, but this was not reflected in their NART IQ. The average 17-item Hamilton score was 23·5 (S.D. = 7·6, range = 8–45) in the depressed group, the mean Newcastle score 6·9 (S.D. = 2·28, range = 2–11). Four of the 15 patients had obvious retardation (Hamilton score of 2+). One patient was not able to co-operate with the whole scanning sequence, and was, therefore, not included in the analysis of imaging data.

Psychometric testing

As expected, patients reported more depression and fatigue than controls (Table 1). Patients were weaker than controls in the hand grip task, and tended to be slower for total reaction time, response initiation time, and movement time. There were no differences between patients and controls for state anxiety and for neuropsychological tests, apart from a trend for poorer verbal fluency in patients.

IBZM binding and diagnosis

Fig. 1 shows that depressed patients had higher right striatal activity than controls, using whole slice as a reference region (mean: 1·68 (S.D. = 0·08) *v.* 1·62 (0·07), Cohen's $d = 0·8$; Mann–Whitney *U* test: $Z = 1·8$, $P = 0·03$). There was no significant effect on the left side (1·66 (0·08) *v.* 1·63 (0·09), $d = 0·4$; Mann–Whitney *U* test: $Z = 0·7$, $P = 0·23$). Frontal uptake indices produced essentially identical, albeit slightly more pronounced, group effects (right: 1·88 (0·13) *v.* 1·77 (1·00), Cohen's $d = 1·0$; Mann–Whitney *U* test: $Z = 2·3$, $P = 0·01$; left: 1·88 (0·18) *v.* 1·80 (0·12), Cohen's $d = 0·5$; Mann–Whitney *U* test: $Z = 1·6$, $P = 0·05$). The near significant group difference for frontal IBZM uptake ratios of the left striatum together with the increase in effect size from whole slice to frontal ratios for both sides, suggests that left striatal increases in IBZM binding are a real effect that requires larger samples to be statistically confirmed.

Table 1. *Descriptive and clinical variables in depressed patients and healthy volunteer controls*

Variable	Depressed ($N = 14$) Mean (S.D.)	Controls ($N = 15$) Mean (S.D.)	Mann–Whitney *U* test *P*
Age (years)	45 (14)	41 (10)	0·54*
Sex (M/F ratio)	9/6	9/6	
NART IQ	112 (10)	116 (7)	0·24*
Education (years)	13 (3)	15 (2)	0·07*
APSAQ	9 (8)	5 (4)	0·24
BFS			
Total	26 (14)	9 (8)	0·002
Mood	6 (5)	1 (2)	0·01
Fatigue	6 (5)	2 (3)	0·004
Isometric contraction (kg)	34 (15)	45 (14)	0·03
Total reaction time (ms)	684 (227)	571 (63)	0·06
Response initiation time (ms)	524 (168)	449 (47)	0·09
Movement time (ms)	488 (353)	330 (58)	0·05
Digit symbol substitution test	10 (2)	11 (2)	0·15
Trails A (s)	32 (7)	32 (9)	0·49
Trails B (s)	90 (108)	54 (17)	0·25
Verbal fluency (words/3 min)	39 (20)	48 (10)	0·09
AVLT total (5 trials)	49 (15)	55 (8)	0·24
Delayed recall	10 (4)	12 (3)	0·31
Recognition	12 (6)	13 (3)	0·29

* Two-tailed *P* values.

IBZM binding and potential confounders of diagnosis

Across both groups, women had higher striatal (whole slice) uptake ratios compared with men for both the left (1·68 (S.D. = 0·07) *v.* 1·61 (S.D. = 0·08), $d = 0·9$) and the right side (1·69 (S.D. = 0·06) *v.* 1·62 (S.D. = 0·09), $d = 0·9$). Although

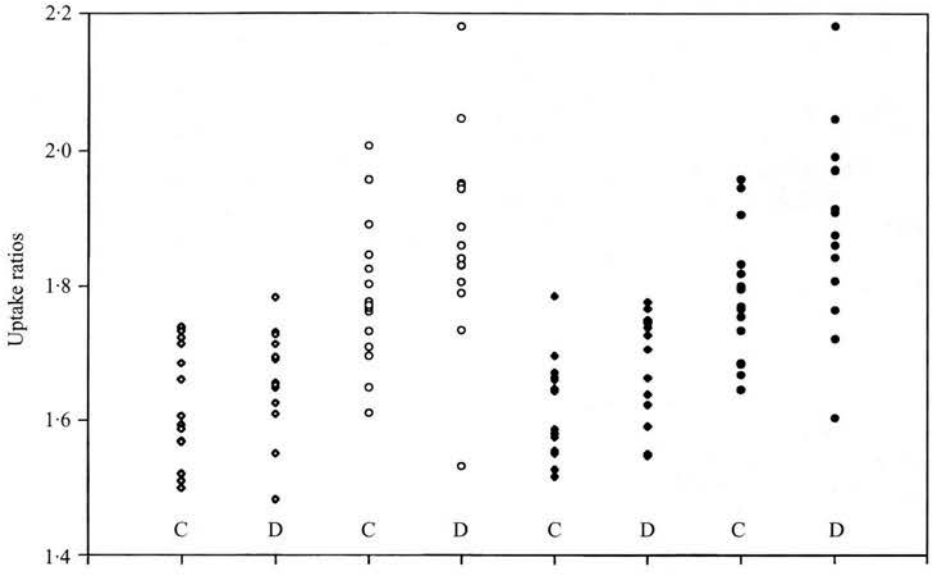

FIG. 1. Right (◆) and left (◇) whole slice and right (●) and left (○) frontal striatal uptake ratios for IBZM in depressed patients (D) and healthy volunteer controls (C).

Table 2. *Spearman's rho correlations with right and left whole slice striatal uptake ratios of IBZM in depressed patients*

	Right		Left	
	Rho	95% CI	Rho	95% CI
Age	−0·22	−0·62 to 0·27	−0·24	−0·63 to 0·25
NART IQ	0·15	−0·33 to 0·57	0·13	−0·35 to 0·56
Hamilton scale	−0·20	−0·60 to 0·29	−0·18	−0·59 to 0·31
Newcastle scale	0·03	−0·44 to 0·48	0·00	−0·46 to 0·46
APSAQ	0·00	−0·46 to 0·46	−0·07	−0·51 to 0·40
BFS				
Total	−0·09	−0·53 to 0·39	−0·11	−0·54 to 0·37
Mood	−0·05	−0·50 to 0·42	−0·11	−0·54 to 0·37
Fatigue	−0·12	−0·55 to 0·36	−0·06	−0·51 to 0·41
Isometric contraction	0·00	−0·46 to 0·46	0·01	−0·45 to 0·47
Retardation (HAM)	0·21	−0·28 to 0·61	0·19	−0·30 to 0·60
Reaction time (total)	0·27	−0·22 to 0·65	0·26	−0·23 to 0·64
Response initiation	0·04	−0·43 to 0·49	0·03	−0·44 to 0·48
Movement time	0·59**	0·18 to 0·83	0·60**	0·19 to 0·83
DSST	−0·04	−0·49 to 0·43	−0·04	−0·49 to 0·43
Trails-A	−0·08	−0·52 to 0·39	−0·04	−0·49 to 0·43
Trails-B	−0·05	−0·50 to 0·42	−0·07	−0·51 to 0·40
Verbal fluency	−0·56**	−0·81 to −0·13	−0·52*	−0·80 to −0·09
AVLT (total)	0·14	−0·34 to 0·56	0·18	−0·31 to 0·59
Delayed recall	0·24	−0·25 to 0·63	0·30	−0·19 to 0·67
Recognition	0·01	−0·45 to 0·47	−0·01	−0·74 to 0·45

*$P < 0·05$; **$P < 0·02$.

this effect of sex appeared to be greater in healthy volunteers ($d = 0·9$–$1·5$) than in depressed patients ($d = 0·1$–$0·4$), there was no significant diagnosis by sex interaction ($F_{4,22} = 0·49$; $P = 0·75$). Since both groups had equal ratios of males to females, sex was ignored as a

confounding variable for the group comparison. Female patients were more retarded than male patients (1·8 (S.D. = 0·98) *v.* 0·75 (S.D. = 0·71; Mann–Whitney *U* test, $P = 0{\cdot}04$), but otherwise male and female patients were well matched for the items and the total score of the Hamilton scale, the Newcastle scale and age.

We examined the effect of concomitant medication that could potentially decrease dopaminergic activity in an indirect fashion (such as antidepressants and benzodiazepines), by comparing ten patients on medication with the four patients off medication. There was no significant effect, although the actual effect sizes observed were large ($d = 0{\cdot}85$–$0{\cdot}95$) with higher IBZM binding in medicated patients, and therefore deserve further investigation as a possible confounder of diagnosis. Not surprisingly, a comparison of patients on ($N = 7$) and off ($N = 7$) antidepressants (including lithium) yielded very similar results ($d = 0{\cdot}80$–$0{\cdot}99$).

Correlations between clinical and neuropsychological scales

There were positive correlations of total reaction time ($\rho = 0{\cdot}77$, $P = 0{\cdot}001$, 95% CI = 0·50 to 0·90), response initiation time ($\rho = 0{\cdot}74$, $P = 0{\cdot}001$, 95% CI = 0·44 to 0·89), and movement time ($\rho = 0{\cdot}48$, $P = 0{\cdot}04$, 95% CI = 0·05 to 0·76) with endogenicity of the depressive illness, as measured by the Newcastle scale. Reaction times did not correlate with depression severity, as estimated by the Hamilton scale total. Total reaction time ($\rho = 0{\cdot}47$, $P = 0{\cdot}04$, 95% CI = 0·03 to 0·76) and response initiation time ($\rho = 0{\cdot}51$, $P = 0{\cdot}03$, 95% CI = 0·09 to 0·78) were, however, positively correlated with retardation on the Hamilton scale. Maximal isometric contraction also correlated with the Newcastle scale ($\rho = -0{\cdot}56$, $P = 0{\cdot}02$, 95% CI = $-0{\cdot}80$ to $-0{\cdot}16$). Finally, performance on the verbal fluency task showed a trend towards negative correlation with retardation on the Hamilton scale ($\rho = -0{\cdot}39$, $P = 0{\cdot}08$, 95% CI = $-0{\cdot}71$ to 0·06).

Correlation between IBZM uptake and psychometric variables

Table 2 shows the correlations of clinical and psychometric variables with striatal whole slice uptake ratios. We found positive correlations between movement time and regional uptake ratios, as well as negative correlations between verbal fluency and regional uptake ratios in the depressed group. Other measures of clinical retardation, such as the Hamilton-retardation score, response initiation time, and other timed neuropsychological tests were not significantly correlated with IBZM uptake in depressed patients. Notably, there were no correlations between uptake and severity of depression as measured by the Hamilton scale, type of depression as measured by the Newcastle scale, or age of the patient.

An exploratory analysis of the Hamilton items showed that there was a strong negative correlation between the suicide item and IBZM uptake (right $\rho = -0{\cdot}70$, $P = 0{\cdot}002$, 95% CI = $-0{\cdot}88$ to $-0{\cdot}35$; left $\rho = -0{\cdot}63$, $P = 0{\cdot}008$, 95% CI = $-0{\cdot}85$ to $-0{\cdot}24$), suggesting that high suicidality was associated with more normal striatal IBZM uptake. Interestingly, in a subgroup of 11 controls, there were positive correlations between neuroticism and striatal IBZM uptake (right $\rho = 0{\cdot}56$, $P = 0{\cdot}035$, 95% CI = 0·05 to 0·84; left $\rho = 0{\cdot}22$, $P = 0{\cdot}26$, 95% CI = $-0{\cdot}34$ to 0·67) and negative correlations with psychoticism (right $\rho = -0{\cdot}48$, $P = 0{\cdot}06$, 95% CI = $-0{\cdot}80$ to 0·06; left $\rho = -0{\cdot}75$, $P = 0{\cdot}004$, 95% CI = $-0{\cdot}91$ to $-0{\cdot}37$), but no correlations with extraversion (Eysenck & Eysenck 1975), thus partially confirming results previously published by Gray and co-workers (1994). These correlations were repeated using frontal regions as a reference area. The results were essentially the same and are not reported here.

DISCUSSION

Group differences

We were able to confirm that there is higher IBZM binding in the right striatum of depressed patients compared with healthy volunteers. There was a smaller difference in the left striatum, which did not quite reach statistical significance, even if a frontal reference region was used. Importantly, in depressed patients higher IBZM binding was correlated with measures sensitive to reduced speed of motor performance, such as movement time and verbal fluency. Binding was not correlated with mood *per se*, grip strength or memory function.

That IBZM binding is higher in the right striatum of depressed patients has some support from Ebert's studies (Ebert *et al.* 1994, 1996), which showed that (retarded) patients had higher right-sided specific activity during a depressive episode, which normalized with drug treatment and with clinical response to sleep deprivation. The effect size of the group comparison was very similar to that reported in previous studies (Ebmeier & Ebert, 1996), suggesting a moderate, but robust effect. This finding has interesting parallels with SPET cerebral perfusion studies in depression. We have found a lower perfusion of basal ganglia structures in depressed patients compared with controls (Austin *et al.* 1992), which normalised on recovery (Goodwin *et al.* 1993).

IBZM binding differed between the sexes, with women having higher binding. This effect was statistically independent of diagnosis and did not confound the comparison of the sex-matched diagnostic groups. Because the sex effect appeared at least as pronounced within the control the main effect across diagnostic groups was not caused by the chance inclusion of more female retarded patients. A previous study has reported plasma homovanillic acid levels 10–70% higher in female than in male schizophrenic patients and controls, an effect that appeared more pronounced in patients acutely after receiving oral fluphenazine (Koreen *et al.* 1994). Pilowski *et al.* (1994) have found greater left than right striatal uptake of IBZM in female, but not in male healthy volunteers. This difference was absent in schizophrenic patients, who showed greater left striatal uptake in both sexes. Animal studies (Kazandjian *et al.* 1987; Häfner *et al.* 1993) and limited human investigations have suggested modulation of dopamine function by oestrogen levels (Wieck *et al.* 1991; Best *et al.* 1992). The explanation of our findings in terms of reduced pre-synaptic release of dopamine or increased post-synaptic expression of receptors must remain tentative but merits further study.

The difference between depressed patients and controls could be, equally, related to state or trait differences between the groups, or a combination of both. There is previous evidence that striatal IBZM uptake in depression may be state dependent (Ebert *et al.* 1994, 1996). A state effect on the occupancy of $D_{2/3}$ sites by IBZM could be due to reduced striatal dopamine release or to an up-regulation of D_2 receptor density. A number of *in vivo* binding studies with benzamides have shown that decreased dopamine D_2 receptor occupancy can be the acute result of increased dopamine release or turnover (Hall *et al.* 1990; Logan *et al.* 1991; Laruelle *et al.* 1995) and the evidence from sleep deprivation suggests a similarly acute effect not likely to be produced by change in receptor number.

None of the subjects received medication directly acting on dopaminergic receptors, but there is some evidence of interactions of other neurotransmitter systems with dopamine function. Serotonergic agonism reduces extrastriatal dopamine concentration, while acute serotonergic blockade increases concentrations (Dewey *et al.* 1995). Acute antidepressant treatment with a serotonin reuptake inhibitor or a less specific drug, could therefore be responsible for increased IBZM binding in depressed patients. Similar effects on dopamine ligand binding have been demonstrated using drugs acting specifically on cholinergic and GABA-ergic transmission (Schloesserg *et al.* 1996). Although there were no significant differences in IBZM binding between medicated and unmedicated patients, and an initial investigation of the effects of antidepressant treatments showed a decrease rather than the predicted increase in IBZM binding (Ebert *et al.* 1996), we can not exclude the possibility at this stage that the diagnosis effect may be confounded by serotoninergic, benzodiazepine, or anticholinergic action of the medication prescribed.

Clinical correlations

Only four of the patients were clinically clearly retarded but there were still measurable psychomotor differences between depressed and control patients, most strikingly in movement time and isometric contraction. There were trends ($P < 0{\cdot}1$) also in other reaction time measures and verbal fluency. Maximal isometric contraction, response initiation and movement times were correlated with endogenicity and clinically rated retardation correlated with reaction time and weakly with fluency. These findings accord with the view that motor signs and, specifically, measures of performance may be more discriminating than subjective symptoms for identifying endogenous patterns of illness. It relates to

a long standing tradition that places clinical retardation as the core symptom in depressive illness (Widlöcher, 1983; Parker *et al.* 1993).

Correlations with IBZM uptake

IBZM uptake correlated most strongly with relatively pure measures of motor function (speed of movement in the reaction time task) rather than clinical measures of mood, fatigue, grip strength or even retardation. This was despite the much greater group difference and within group variance for the patients compared with controls in the latter measures. This finding provides the first direct evidence suggesting that reduced receptor occupancy by endogenous dopamine in the basal ganglia has a primary effect on motor function in depression, although some limited evidence already exists to suggest acute reversibility of IBZM binding in depression (Ebert *et al.* 1996). IBZM uptake was also correlated with verbal fluency and showed a trend with DSST performance. These are also tests which depend upon speed of motor performance and showed trends towards impairment in the depressed group. Performance of Trails A and B was neither impaired in the patient group nor correlated with IBZM binding. Since the patients in this study did not on average display major psychomotor impairment, the correlations that did emerge were striking. Significant correlations could only be expected for the most sensitive of the measures or for those most directly related to striatal function. In this regard the failure of mood to correlate with striatal IBZM binding is very interesting.

The strong negative correlation of IBZM uptake with suicidality could not be explained by sex differences and was otherwise unexpected. It could reflect the anecdotal clinical observation that activated depressed patients are at increased risk of suicide; this occurs classically after alleviation of psychomotor retardation by treatment, without an improvement of affect. Finally, the finding of relatively abnormal IBZM uptake in controls with high neuroticism and low psychoticism is of interest, because neuroticism is a strong predictor of later depressive breakdown (Hirschfeld & Klerman, 1979; Angst & Clayton, 1986; Hirschfeld *et al.* 1986). It means that the potential contribution of trait differences to increased IBZM binding should not yet be discounted for depressive illness. We were also able to replicate the result of Gray *et al.* (1994), who found a significant negative correlation of psychoticism with IBZM binding in left and right striatum, which they suggest may be due to an association between increased dopaminergic activity with receptor down regulation and psychosis-prone normal individuals. This interpretation is somewhat at variance with the reported increase in B_{max} for N-methyl-spiperone binding in psychotic bipolar patients during positron emission tomography (Pearlson *et al.* 1995). This discrepancy could be due to a variety of causes ranging from the different spectrum of DA receptors labelled by benzamides and spiperone, to relative displacement by the endogenous agonist dopamine, to the effect of diagnosis (healthy *versus* manic–depressive; 'pre-psychotic' *versus* psychotic), and least likely to previous medication, because all but three of Pearlson's 14 patients were neuroleptic naive (Pearlson *et al.* 1995).

CONCLUSION

This study has identified a difference in the specific binding of IBZM in striatum between males and females. In previous studies of depression, the samples have either been all male (D'haenen & Bossuyt, 1994) or of unequal sex ratios (Ebert *et al.* 1994, 1996). Sex will, therefore, have to be controlled for as a confounder in future studies. Depressed patients showed a modest but significant percentage increase in striatal binding of IBZM. Increased binding is probably associated with a reduction in dopaminergic function either reflected in reduced dopamine release and/or dopamine receptor up-regulation. Striatal binding in the depressed patients was correlated with motor slowing and not with mood, fatigue or hand grip. The observed associations between dopamine receptor binding and the motor slowing of the depressed state may, at least in part, reflect a more stable trait of depressed patients.

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Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression

Controlled magnetic resonance imaging study

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Background The aetiology of treatment-resistant major depression is little understood; its apparent intractability may reflect brain abnormality.

Method Magnetic resonance images of the brains of 20 subjects with major depression lasting for two years or more were compared with 20 healthy control subjects and 20 other subjects who had completely recovered from depression. Subjects were individually matched for age, gender, years of education and premorbid IQ. Grey matter was segmented from the images, and compared between groups on a voxel-by-voxel basis.

Results Subjects with chronic depression showed reduced grey matter density in the left temporal cortex including the hippocampus. There was also a trend for reduction in the right hippocampus. Left hippocampal grey matter density was correlated with measures of verbal memory, supporting the functional significance of the observed magnetic resonance imaging changes.

Conclusions Our results potentially challenge the accepted view of depression as a functional and fully reversible illness, implying instead that more permanent brain changes may be associated with chronicity. Confirmatory longitudinal and prospective studies are required to determine whether these differences pre-date the onset of depression or are the result of the chronic illness process or its treatment.

While major depression is generally regarded as a reversible psychiatric illness without lasting changes in the brain, it actually follows a more chronic, treatment-resistant course in up to 20% of subjects (Keller *et al*, 1982). Such a course implies that some permanent changes to the brain may have occurred, but previous neuroimaging studies have either ignored the issue or provided only limited evidence for biological correlates (Morinobu *et al*, 1991). Hippocampal atrophy has been found in the aftermath of highly stressful life periods, and notably in a small cohort of elderly depressed subjects with recurrent depression (Bremner *et al*, 1995; Sheline *et al*, 1996; Stein *et al*, 1997). In our present study we use a novel voxel-based analysis of magnetic resonance imaging (MRI) scans to compare cortical grey matter density between younger subjects with treatment-resistant chronic depression, matched recovered subjects and normal healthy volunteer subjects.

METHOD

Subjects

Twenty subjects with treatment-resistant depression, aged between 21 and 65, fulfilling DSM–IV (American Psychiatric Association, 1994) criteria for major depressive disorder (chronic) were recruited from general adult in-patient units and from out-patient clinics in Lothian. The subjects also fulfilled Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978) for a primary major depressive disorder. Chronicity was defined by a diagnosis of major depressive episode (DSM–IV) lasting for two or more years continuously. Treatment resistance was assumed if the subjects did not respond to at least two treatments from the following four different pharmacological regimes employed for at least four weeks:

(a) 150 mg of imipramine or an equivalent tricyclic antidepressant;

(b) 60 mg of phenelzine or an equivalent monoamine oxidase inhibitor;

(c) 40 mg of fluoxetine or an equivalent selective serotonin reuptake inhibitor;

(d) six treatments with electroconvulsive therapy (ECT) with seizures >20 seconds each.

All the subjects with chronic depression were on a stable medication for at least two weeks prior to the study, as it was not possible to study the subjects medication free. The subjects with chronic depression had not received electroconvulsive therapy (ECT) for at least three months. Twelve subjects had required at least one psychiatric admission.

Twenty subjects who had recovered from depression previously fulfilling the DSM–IV criteria for a major depressive disorder, and 20 normal healthy volunteer subjects (recruited from hospital secretarial and nursing staff, as well as community volunteers) were also examined. Subjects from both these groups were individually matched with the subjects with chronic depression for age, gender, intelligence and years of education. Subjects who had recovered from depression were matched, for age of onset and for onset of the index episode, with the chronic depression group. Recovery was defined as scoring five or less on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) for at least three months prior to the study. The subjects who had recovered from depression were either on a stable medication for at least two weeks prior to the study, or were medication free.

All subjects were interviewed using the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L; Endicott & Spitzer, 1978). Case notes were reviewed in detail, providing RDC diagnoses and allowing lifetime histories of psychiatric illness to be determined. Treatment histories were re-constructed from case notes and from interview. Healthy volunteers had no lifetime history of significant psychiatric illness, using the SADS-L interview schedule. Exclusion criteria for all groups were: previous manic episodes; organic cerebral pathology; neurological illness; significant alcohol or substance misuse; head injury associated with significant loss of consciousness; hypothyroidism or concurrent use of exogenous steroids.

All subjects gave informed written consent following a protocol approved by the local research ethics committee.

Neuropsychological and clinical assessment

All subjects underwent neuropsychological and clinical testing in a standardised environment, within a two-day period. Symptom severity was measured using the HDRS and cerebral dominance indexed using a handedness scale (Annett, 1970). Subjects performed the revised National Adult Reading Test (NART; Nelson & Willison, 1991) to measure premorbid IQ, and a battery of neuropsychological tests, including the Auditory Verbal Learning Test (AVLT; Lezak, 1983), a measure of verbal learning and memory. A dexamethasone suppression test was given to all subjects within the week after all clinical, and neuropsychological testing and imaging was completed.

Magnetic resonance image acquisition and analysis

Analysing structural scans usually involves laborious slice by slice measurement of local structures. The use of voxel-based analysis has only recently been extended to the analysis of structural MRI (Wright *et al*, 1995), although it has transformed the approach to isotope and MRI-based functional imaging (Friston *et al*, 1995*a*,*b*). MRI scans of subjects are compared after spatial transformation into a standard brain atlas space to remove variation in overall brain position, size and shape. Subsequent to segmentation of the images, grey or white matter compartments may be compared between groups on a voxel by voxel basis. The technique for spatially transforming and segmenting images into different tissue types is fully automated and operator-independent.

All subjects were scanned within one week of the clinical assessment. Magnetic resonance images were acquired on a Siemens 1 Tesla system, using a magnetisation prepared rapid acquisition graded echo (MPRAGE) sequence, with images acquired perpendicular to the anterior-to-posterior commissure line. This sequence produces high resolution images with good contrast between white and grey matter (TR=10 ms, TD=500 ms, flip angle=12°, block size=240 mm, 128 contiguous slices with an effective slice thickness of 1.875 mm). Image analysis was performed on a SPARC workstation (Sun Microsystems Europe Inc) using ANALYZE (CNS Software), and SPM '96 for spatial normalisation and statistical parametric mapping (Friston *et al*, 1995*a*,*b*) running in MATLAB (The Mathworks Inc).

In ANALYZE, images were first corrected for field inhomogeneities with a phantom image using image algebra, then converted to 8-bit images and flipped to reverse right and left to comply with the neurological convention. Within the SPM '96 software, images were first spatially normalised into standard space and then segmented into grey matter, white matter, cerebrospinal fluid (CSF) and skull/scalp compartments, using an automated and operator-independent process. Spatial normalisation involved reading image data in coronal orientation and linearly deforming them using a 12-point affine transformation to fit a T_1-weighted template image which included skull and scalp. Nearest neighbour interpolation was used to preserve tissue type boundaries and the original intensity spectrum of the image. The normalised image has a voxel resolution of $1 \times 1 \times 2$ mm. Images were then segmented using a modified clustering algorithm based on the maximum likelihood 'mixture model' (Hartigan, 1975) which allows classification of tissue type, as well as tissue density. The algorithm uses a combination of the underlying multi-normal distribution of T_1 relaxation times, and a series of *a priori* probability images for each tissue type, where each voxel represents the prior probability of tissue at a location belonging to a particular compartment. The multi-normal distribution reflects the distinct T_1 intensity clusters from different tissue types, with the key assumption that the range of T_1 relaxation times from the image produce a range of intensities which reflect different tissue types and, within each distribution, different tissue densities. *A priori* segmented probability images provide approximate spatial distributions of different tissue types. These were derived from averaging the spatially transformed segmented images of grey, white matter and CSF from MRIs of healthy volunteers. The intensity distribution of the probability image ranges between 0 and 1. The algorithm is iterative and has the effect of biasing voxel classification towards the *a priori* distribution. Prior to statistical comparison, the spatially normalised segments were smoothed with a 12 mm full width at half maximum isotropic Gaussian kernel to remove variation due to individual differences in sulcal and gyral patterns. The segmentation procedure used in this study is more sophisticated than the method previously applied by Wright *et al* (1995). Grey matter is classified having continuous values from 0–1 based on probability, whereas the earlier technique classified tissue only as 0 to 1, in binary fashion. In addition, by smoothing the data, the partial volume effect is used to convert differences in the amount of grey matter locally into differences in intensity. For reasons of economy, only grey matter results are reported in this paper.

Statistical comparison

An ANCOVA model was applied which removed global grey matter density for each subject. This normalises the transformed and segmented brain image to the same total amount of grey matter, while preserving regional differences in grey matter density. Age-effects were also removed by ANCOVA. Differences between groups were displayed as statistical parametric maps (SPMs), with a threshold probability of 1%. Statistical clusters were projected on to a T_1-weighted grey matter density template to facilitate interpretation of the results. Corrected probability values were computed which take into account the whole volume examined, the smoothness of the data, the size of the cluster with $P<0.01$, and the peak effect (Z-value). Group demographic and clinical data were compared using univariate ANOVA and *post hoc* t-tests to identify specific group differences. Non-continuous variables were compared using the Kruskal–Wallis and Mann–Whitney U and χ^2 tests, as appropriate. The latter statistics were computed using SPSS version 4.0 for the Macintosh.

RESULTS

Clinical data

The three groups did not statistically differ in age, gender, cerebral hemispheric laterality, years of education, estimated premorbid IQ and the total number of years smoking (Table 1), although there was a tendency for the subjects with chronic depression to have fewer years of education, a lower NART IQ and perhaps to be right-lateralised to a lesser degree. The mean age of onset of first and most recent episodes of depression did not differ between the chronic and

recovered groups. Subjects with chronic depression had suffered a longer duration of illness and longer illness episodes. Within the chronic depression group, all were taking antidepressant drugs. In addition, 12 subjects with depression took regular neuroleptic medication, five took lithium and three benzodiazepines. Fourteen subjects with depression had received ECT in the past. Nine of the subjects who had recovered from depression were prescribed antidepressants, one also received neuroleptics and one lithium. Eleven of the subjects who had recovered from depression had previously received ECT. Subjects with chronic depression had moderately severe depressive symptoms (17-item HDRS, mean 20.6, s.d.=5.3, range 10–30). Subjects who had recovered from depression had been well for a mean period of 136 weeks (s.d.=83; range: 43–290), 16 had previously required in-patient treatment. Only one depression-recovered subject would previously have qualified for a diagnosis of chronic depression (duration of episode: 182 weeks). The chronic depression group performed more poorly on the AVLT delayed recognition test (mean=8.2, s.d.=4.8) in comparison with both depression-recovered subjects (mean=13.4, s.d.=1.4) and control subjects (mean=12.3, s.d.=2.8; $F(2,55)=13.29$, $P<0.0001$). Post-dexamethasone morning and afternoon cortisol values did not differ between the three groups. Median values for subjects with chronic depression, depression-recovered and control subjects were 16.0, 21.6 and 24.0 nmol/l ($\chi^2=4.1$, $P=0.13$, corrected for ties) and 16.5, 21.1 and 23.4 nmol/l ($\chi^2=0.3$, $P=0.85$) respectively. Values ranged between 16.0 and 44.6 nmol/l (0.58–1.61 μg/dl) in the morning, and 16.0 and 82.4 nmol/l (0.58–2.97 μg/dl) in the afternoon, that is, all subjects were suppressors.

Grey matter density

Fig. 1 shows grey matter density reductions in subjects with chronic depression compared with healthy control subjects. Reductions were found over large areas of the left temporal neocortex and left anterior hippocampus (Table 2). Comparison of subjects with chronic depression with depression-recovered subjects yielded very similar results. Subjects who had recovered depression and control subjects showed no significant differences in grey matter density. We also found an apparent increase in cuneus/precuneus grey matter density in the subjects with chronic depression compared with both subjects who had recovered from depression and the control subjects. This may reflect the consequences of the left hemispheric changes on grey matter values in the former group with relatively normal cuneus/precuneus grey matter. As there was an *a priori* hypothesis linking verbal memory with left temporal lobe function, we correlated grey matter density with performance on the AVLT delayed recognition test in the chronic group. Left hippocampal grey matter density was positively correlated with recall of previously learnt verbal material (Fig. 2 and Table 3).

DISCUSSION

Grey matter abnormalities in chronic depression

We were able to demonstrate that middle-aged unipolar subjects with treatment-resistant chronic depression had reduced grey matter density in large areas of the left temporal cortex, including left anterior hippocampus, compared with both healthy control subjects and subjects who had recovered from depression. Well matched depression-recovered subjects did not differ from healthy control subjects. We chose to examine subjects who were symptomatic for two years or more, in line with the definition of chronicity proposed in DSM–IV. In fact, our sample of subjects with chronic depression well exceeded two years of active illness, having a mean episode duration of 197 weeks. This result adds to the evidence accumulating that, in elderly patients, chronicity may be associated with increased ventricle to brain ratio (Roy-Byrne *et al*, 1988), with decreased temporal (Altshuler, 1993) and amygdala–hippocampal volume (Axelson *et al*, 1993; Sheline *et al*, 1996), as well as the observation that chronic or overwhelming stress may be associated with hippocampal atrophy (Bremner *et al*, 1995; Stein *et al*, 1997).

Functional correlates of grey matter abnormalities

In agreement with a previous study in chronic bipolar illness (McKay *et al*, 1995), verbal recognition was significantly impaired in the subjects with chronic depression in our study and, within the group, was correlated with reduced left hippocampal grey matter density. Episodic memory depends on the integrity of the temporal lobes (Mayes & Downes, 1997). Harvey *et al* (1997) compared cognitive function in poor-outcome hospitalised geriatric patients with affective disorders and hospitalised patients with chronic

Table 1 Clinical and descriptive measures (s.d.)

	Treatment-resistant depression group (n=20)	Recovered from depression group (n=20)	Control subject group (n=20)	$F_{2,57}$-probability
Mean age	48.9 (9.8)	47.7 (9.9)	49.3 (11.8)	0.89
Handedness score	13 (16)	16 (13)	19 (5)	0.27
Years of education	11.7 (2.9)	13.4 (3.4)	13.5 (2.9)	0.12
National Adult Reading Test IQ	107 (12.7)	113 (10.2)	115 (8.7)	0.06
Male: female ratio	13:7	13:7	13:7	
Total years smoking	20 (13.6)	12 (13.7)	17 (3.7)	0.14
Age at onset of first episode	38.9 (13.5)	38.2 (10.1)		0.89
Age at onset of last episode	45.8 (10.1)	44.8 (9.8)		0.76
Longest duration of episode (weeks)	197 (125)	46 (36)		<0.001
Lifetime total illness duration (weeks)	263 (133)	76 (58)		<0.001

Table 2 Comparison of grey matter density between diagnostic groups

Effect	Region	Peak coordinates	Peak Z (uncorrected P-value)	Cluster volume, cm^3 (uncorrected P-value)	Corrected P-value
Reduced in chronically depressed v. control subjects	Left superior temporal/ lateral inferior frontal gyrus	−64, −23, 6	4.46 (<0.001)	19.61 (<0.0001)	0.002
		−55, 14, 14	4.07 (<0.001)		
		−56, 1, 32	3.99 (<0.001)		
	Left hippocampus/ inferior temporal gyrus	−29, −18, −16	3.33 (<0.001)	4.56 (0.004)	0.14
		−53, −66, −8	3.13 (0.001)		
	Right hippocampus	31, −25, −12	2.94 (0.002)	1.40 (0.08)	0.84
Reduced in chronically depressed subjects v. depression-recovered subjects	Left superior temporal/ lateral inferior frontal gyrus	−58, −16, 38	3.9 (<0.001)	11.86 (<0.001)	0.009
		−66, −28, −14	3.7 (<0.001)		
		−64, −23, 8	3.6 (<0.001)		
	Left hippocampus/ parahippocampal gyrus	−38, −16, −28	4.42 (<0.001)	5.56 (0.002)	0.08
		−25, −30, −8	3.97 (<0.001)		
		−32, −20, −20	3.9 (<0.001)		
	Right hippocampus/ parahippocampal gyrus	30, −21, −18	3.1 (0.001)	1.36 (0.08)	0.85
		29, −29, −12	3.0 (0.001)		
		17, −11, −16	2.65 (0.004)		
Reduced in control v. chronically depressed subjects	Left cuneus/precuneus	−8, −72, 0	3.92 (<0.001)	12.88 (<0.001)	0.007
		−4, −52, 34	3.72 (<0.001)		
		−16, −86, 24	3.71 (<0.001)		
	Right cerebellum	40, −45, −32	3.37 (<0.001)	5.57 (0.002)	0.08
		21, −30, −28	3.3 (<0.001)		
		29, −31, −26	3.27 (0.001)		
	Left cerebellum	−40, −50, −34	3.24 (0.001)	5.35 (0.002)	0.09
		−35, −43, −32	3.24 (0.001)		
		−28, −27, −26	3.22 (0.001)		
Reduced in depression-recovered v. chronically depressed subjects	Right cuneus/precuneus	−12, −89, 22	4.44 (<0.001)	33.04 (<0.001)	0.001
		−4, −53, 34	4.39 (<0.001)		
		−5, −73, 24	4.11 (<0.001)		

Coordinates refer to the voxels with maximum (peak) effect sizes as defined by the brain atlas of Talairach & Tournoux (1988). If multiple coordinates are given, the cluster of contiguous voxels with an uncorrected $P < 0.01$ has multiple peak effect sizes. Uncorrected P-values are given for peak effect sizes and for the cluster volumes of contiguous voxel with uncorrected $P < 0.01$. Corrected P-values have been adjusted for multiple comparisons according to peak effect size, cluster volume, smoothness of data and total volume examined (Friston *et al*, 1995*b*). Results are corrected for age.

Table 3 Regression of grey matter density on performance in delayed verbal recognition (Friston *et al*, 1995*b*), controlling for age in the chronic depression group only (n=19)

Region	Peak coordinates	Peak Z (uncorrected P-values)	Cluster volume, cm^3 (uncorrected P-value)	Corrected P-value
Left hippocampus	−35, −9, −32	4.33 (<0.001)	8.01 (<0.001)	0.04
Parahippocampal	−35, −15, −24	3.31 (<0.001)		
Gyrus	−30, −9, −22	3.30 (<0.001)		

Coordinates refer to the brain atlas of Talairach & Tournoux (1988). The multiple coordinates indicate that the cluster of contiguous voxels with an uncorrected $P < 0.01$ has multiple peak effect sizes. Uncorrected P-values are for peak effect sizes and for the cluster volume of contiguous voxel with uncorrected $P < 0.01$. Corrected P-values have been adjusted for multiple comparisons according to peak effect size, cluster volume, smoothness of data and total volume examined (Friston *et al*, 1995*b*)

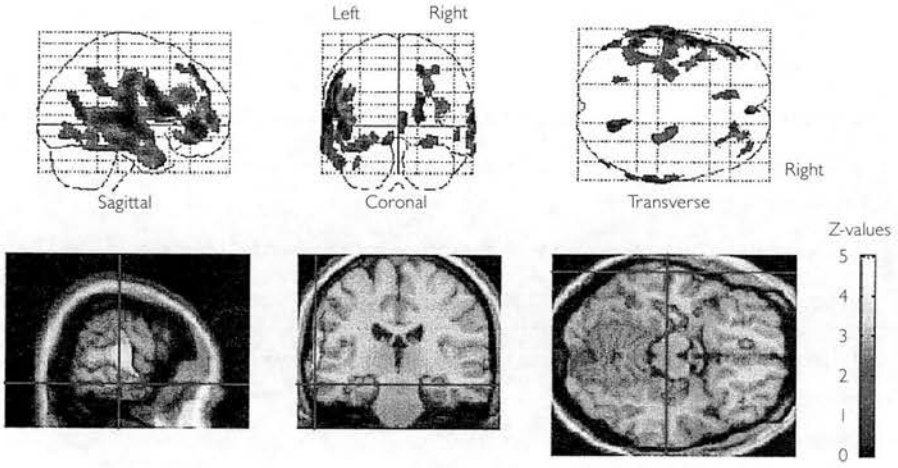

Fig. 1 Statistical parametric maps ($P < 0.01$) for reductions in grey matter densitities in subjects with chronic depression compared with healthy control subjects. Effects are controlled for age.

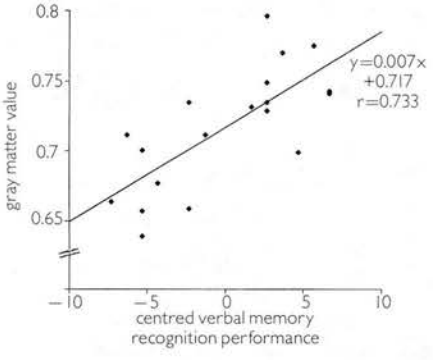

Fig. 2 Positive correlation of grey matter density with delayed verbal recognition, controlling for age and premorbid IQ in a pixel within the left hippocampus (−30 −9 −22). Effects are controlled for age.

schizophrenia and found no group differences, suggesting that the severity of cognitive impairment may correlate with chronicity, regardless of diagnosis. In support of this notion, a correlation of left hippocampal volume with verbal memory performance could be demonstrated in subjects with schizophrenia, who also show reduced hippocampal size (Goldberg *et al*, 1994).

Methodological considerations

This is the first application of a new voxel-based analysis of structural MRI, comparing patient groups and control subjects. Voxel-based analysis is generally likely to be more sensitive to localised differences which may be a small part of, or overlap, the structures (object maps) measured in traditional volumetric approaches (Ebmeier *et al*, 1998). Because the results in this study may, therefore, not be detectable with the traditional 'gold standard' volumetry, an independent replication of the results using statistical parametric mapping or another voxel-based method will be essential. One reason for this is that our measure of grey matter density is based on regional T_1-relaxation times. Changed T_1 at the boundary with other compartments may be due to partial volume effects in the presence of structural brain differences, but local changes in brain chemistry may also affect T_1. Subjects with depression often restrict their food intake and suffer weight loss, which in turn may result in reversible brain atrophy, similar to that observed in anorexia nervosa (Swayze *et al*, 1996), although it is not clear why such atrophy should be localised or lateralised to the left side.

Possible aetiologies of grey matter abnormalities

Grey matter changes can be antecedent to or consequent upon depressive symptoms or their treatment. Obstetric complications may be more frequent in subjects with depression (Guth *et al*, 1993). In schizophrenia, left temporal lobe volume reduction may reflect reduced neurodevelopmental cerebral lateralisation (DeLisi *et al*, 1991). The subjects with chronic depression in our study showed a similar tendency to less lateralisation, implying that neurodevelopmental abnormalities in subjects with unipolar depression, particularly affecting the left temporal lobe, may finally predispose to chronicity.

Alternatively, the chronic illness may be responsible for temporal lobe atrophy. Raised levels of cortisol, which are not suppressed by dexamethasone may predict rapid relapse and possibly chronicity (Amsterdam *et al*, 1983). Animal work suggests that chronically raised cortisol can facilitate hippocampal neuronal death, which in turn may cause dysregulation of the hypothalmic–pituitary–adrenal (HPA) axis (Sapolsky *et al*, 1986). Dysregulation of the HPA axis can also be found in people with schizophrenia, who have reduced hippocampal volumes. However, since temporal lobe damage may cause hypercortisolaemia, these assoiations do not establish the direction of the effect. Interestingly, the subjects with chronic depression did not exhibit dexamethasone non-suppression, suggesting that hypercortisolaemia was not an important factor maintaining chronicity in this sample. However, since we did not obtain baseline measures of cortisol and this was a cross-sectional study, the possibility of present or previous HPA dysfunction cannot be discounted.

Finally, the treatment of depression may be responsible for localised tissue loss. To test this hypothesis, we correlated the number of ECTs during subjects' lifetimes with grey matter density in the chronic depression group. There were no correlations with hippocampal grey, but there were some neocortical regions with significant correlations extending over temporal and frontal lobes. Whether such associations are causal, and if so in which direction is not clear. Longitudinal studies are required to determine whether cortical atrophy predates particularly severe illnesses which require ECT, or whether ECT causes such changes. Although we have very closely matched groups, the study could be criticised for including chronically depressed and depression-recovered subjects who were taking medication. There is no convincing evidence to suggest that long-term antidepressants or ECT are responsible for structural brain changes (Scott *et al*, 1995) or changes in cognitive function greater than those produced by depression. Further, there were no grey matter differences between control subjects and the subjects who had recovered from depression, some of whom were on psychotropic medication and had previously received ECT.

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CLINICAL IMPLICATIONS

- Subjects with chronic depression may have significant memory impairment.
- Subjects with chronic depression may have hippocampal abnormalities related to this memory impairment.
- Subjects who have recovered from depression have normal MRI scans.

LIMITATIONS

- Study design and the method used cannot distinguish between state- and trait-related abnormalities.
- Aetiology of the observed changes is unclear.
- As with all small scale biological studies, these results require independent replication.

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