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TEIJAMARI LAASONEN-BALK

# Neuroimaging of Depression Using Single-Photon Emission Computerized Tomography

Doctoral dissertation

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## ABSTRACT

Depression is a common psychiatric disorder globally. Lifetime prevalence of major depression varies from 5 to 26%. The etiology of depression is a combination of neurobiological and psychosocial factors. Brain regions such as the prefrontal cortex, brain stem structures, the hippocampus, hypothalamus, cingulate and basal ganglia have important roles in the mechanisms of emotion and the influence of the mood.

The aim of this study was to obtain a better understanding of the role of neurotransmitters on the neurobiology of depression. These investigations were performed using single-photon emission computerized tomography (SPECT), using [$^{123}$I]iomazenil in one study and [$^{123}$I]β-CIT in the other three studies.

When thirteen depressed outpatients and seven healthy controls were studied with [$^{123}$I]iomazenil, the patients had significantly lower benzodiazepine receptor densities in both temporal cortices and the prefrontal cortex. A significantly higher striatal dopamine transporter (DAT) density was found in fifteen drug-free depressed patients compared with eighteen healthy controls. This finding could be explained by concluding that up-regulation of DAT may be the primary alteration, which leads to a lower intrasynaptic dopamine concentration and lower dopamine neural transmission. Cluster C personality disorder had no independent effect on DA transmission as reflected by DAT density.

The results of the longitudinal comparison of drug-free patients before and after recovery from depression indicate that the patients who recovered had a significantly greater increase in [$^{123}$I]β-CIT binding in the midbrain than non-recovered patients. This clinically important result might imply that serotonin transporter (SERT) density in the midbrain increases during recovery from depression.

According to the findings of these brain imaging studies, it can be assumed that depression is associated with CNS dysfunction. Our findings emphasize the importance of active treatment of depression, not only for its psychosocial effects but also due to its positive effect on CNS function.

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Medical subject headings: depression; depressive disorder; depressive disorder, major; personality disorder; neurotransmitters; neurobiology/methods; tomography, emission-computed, single-photon

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## TIIVISTELMÄ

Masennus on maailmanlaajuisesti yleinen psykiatrinen sairaus. Vakavan masennuksen elinikäinen esiintyvyys vaihtelee otoksesta riippuen 5-26 % välillä. Masennuksen taustalla on yhdistelmä neurobiologisia ja psykososiaalisia tekijöitä. Useilla aivoalueilla, kuten etuotsalohkon kuorikerroksella, aivorungon alueilla, hippocampuksella, hypothalamuksella, cinguluksella ja tyvitumakkeilla, on tärkeä merkitys tunne-elämän mekanismien muodostumisessa sekä mielialojen vaihtelussa.

Tämän tutkimuksen tavoitteena oli selvittää aivojen välittäjäaineiden merkitystä masennuksen neurobiologiassa. Tutkimukset tehtiin käyttäen kuvantamismenetelmänä yksifotoniemissiotietokonetomografiaa (SPECT). Merkkiaineena oli [$^{123}$I]iomazenil ensimmäisessä tutkimuksessa ja muissa kolmessa käytettiin [$^{123}$I]β-CIT merkkiainetta.

Potilailla oli merkitsevästi matalampi bentsodiatsepiini reseptoritiheys molemmilla ohimo- ja etuotsalohkoaivokuorialueilla, kun kolmetoista masentunutta avohoitopotilasta ja seitsemän tervettä kontrollihenkilöä tutkittiin [$^{123}$I]iomazenil merkkiaineella. Striataalinen dopamiinitransportteri (DAT) tiheys oli merkitsevästi korkeampi viidellätoista lääkkeettömällä masennuspotilaalla verrattuna kahdeksaantoista terveeseen kontrollihenkilöön. DAT:n voimistussäätely (up-regulaatio) voi olla ensimmäinen muutos, mikä johtaa matalampaan soluvälitilan dopamiinipitoisuuteen ja matalampaan dopamiinihermovälitykseen. Cluster C persoonallisuushäiriöllä ei havaittu itsenäistä vaikutusta DA-hermovälitykseen, kun tutkittiin DAT tiheyttä tyvitumakkeissa.

Seurantatutkimuksessa verrattiin lääkkeettömiä masennuspotilaita ennen ja jälkeen kliinisen toipumisen. Toipuneilla potilailla [$^{123}$I]β-CIT:n sitoutuminen keskiaivoihin oli merkitsevästi lisääntynyt verrattuna kliinisesti toipumattomiin. Tämä kliinisesti tärkeä löydös osoittaa, että serotoniinitransportteri (SERT) tiheys keskiaivoissa voi lisääntyä - mahdollisesti palautua ennalleen - masennuksesta toipuessa.

Aivojen kuvantamistutkimuslöydösten perusteella on ilmeistä, että depressioon liittyy keskushermoston toimintahäiriö. Saamamme löydökset painottavat depression aktiivisen hoidon tärkeyttä arvioituna myös keskushermoston toiminnan kannalta.

Yleinen suomalainen asiasanasto: keskushermosto – toiminta – häiriöt; masennus; neurobiologia; persoonallisuushäiriöt; toipuminen; tomografia

*To my family*

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Lappeenranta, January 2005

Teijamari Laasonen-Balk

## ABBREVIATIONS

| | |
|---|---|
| AMPA | α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid |
| APSAQ | Alderley Park State Anxiety Questionnaire |
| ASP | Antisocial personality disorder |
| AVLT | Auditory Verbal Learning Test |
| BDI | Beck Depression Inventory |
| BDNF | Brain-derived neurotrophic factor |
| BFS | Befindlichkeitsskala |
| CA3 | Region in the hippocampus (Cornu Ammon) |
| CAS | Clinical Anxiety Scale |
| CBF | Cerebral blood flow |
| CDI | Children Depression Inventory |
| CGI | Clinical Global Improvement Scale |
| CIDI | Composite International Diagnostic Interview |
| CNS | Central nervous system |
| COMT | Catechol-O-methyl transferase |
| CREB | cAMP response element binding protein |
| C-SSAGA | Child Semi-Structured Assessment for the Genetics of Alcoholism |
| DA | Dopamine |
| DAT | Dopamine transporter |
| DMS | Diagnostic Melancholia Scale |
| DOPA | Dihydroxyphenylalanine |
| DOPAC | Dihydroxyphenylacetic acid |
| DSM-III-R | Diagnostic and statistical manual of mental disorders, version number III-R |
| DSST | Digit Substitution Test |
| ECA | Epidemiologic Catchment Area study |
| ECT | Electric convulsive therapy |
| ES | Effect size |
| fMRI | Functional magnetic resonance imaging |
| GABA | Gamma-aminobutyric acid |
| GAD | Global Anxiety Disorder |
| GAF | Global Assessment of Functioning Scale |
| GAS | Global Assessment Scale |
| G protein | Guanine nucleotide triphosphate binding protein |
| GSS | Global Seasonality Score |
| GTP | Guanine nucleotide triphosphate |
| HAM-A | Hamilton Anxiety Scale |
| HAS | Hamilton Anxiety Scale |
| 5-HIAA | 5-hydroxyindoleacetic acid |
| HRSD | Hamilton Rating Scale for Depression |
| 5-HT | 5-hydroxytryptamine |
| 5-HTP | 5-hydroxytryptophan |
| 5-HTT | Serotonin transporter |
| 5-HTTLPR | Serotonin transporter promoter gene region |
| HVA | Homovanillic acid |
| ICD-10 | International Classification of Diseases and Related Health Problems, $10^{th}$ revision |
| LC | Locus coereleus |
| L-DOPA | L-dihydroxyphenylalanine |
| MADRS | Montgomery-Åsberg Depression rating Scale |
| MAO | Monoamine oxidase |

| | |
|---|---|
| MD | Major depression |
| MHPG | 3-methoxy-4-hydroxy-phenethyleneglycol |
| MMSE | Mini Mental State Examination |
| MRI | Magnetic resonance imaging |
| mRNA | Messenger ribonucleic acid |
| MRS | Magnetic resonance spectroscopy |
| 3-MT | 3-methoxytyramine |
| MPD | Multiple personality disorder |
| NA | Noradrenaline |
| NAA | N-acetylaspartate |
| NC | Normal controls |
| NCS | National Comorbidity Survey |
| NE | Norepinephrine |
| NEMESIS | Netherlands Mental Health Survey and Incidence Study |
| NET | Norepinephrine transporter |
| NMDA | N-methyl-D-aspartate |
| NO | Nitric oxide |
| OCD | Obsessive-compulsive disorder |
| ODIN | Outcome of Depression International Network |
| PCP | Phencyclidine |
| PD | Personality disorder |
| PET | Positron emission tomography |
| rCBF | Regional cerebral blood flow |
| RDC | Research Diagnostic Criteria |
| RN | Raphe nuclei |
| ROI | Regions of interest |
| SAD | Seasonal affective disorder |
| SADS | Schedule for Affective Disorders and Schizophrenia |
| SAD-L | Schedule for Affective Disorders and Schizophrenia - Lifetime version |
| SAI | Stress Arousal Inventory |
| SCAN | Schedules for Clinical Assessment in Neuropsychiatry |
| SCID | Structured Clinical Interview for DSM-III-R |
| SCL | Symptom checklist |
| SD | Standard deviation |
| SERT | Serotonin transporter |
| SIGH-SAD | Structured Interview for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version |
| SPAQ | Seasonal Pattern Assessment Questionnaire |
| SPD | Schizotypal Personality Disorder |
| SPECT | Single-photon emission computerized tomography |
| SSRI | Selective serotonin reuptake inhibitor |
| TAS | Toronto Alexithymia Scale |
| TrkB | Tropomyosin-related kinase receptor B, which belongs to tyrosine kinase receptor family. BDNF is specific for TrkB. |
| VMA | Vanilylmandelic acid |
| VTA | Ventral tegmental area |
| WCST | Wisconsin Card Sort Test |

## LIST OF THE ORIGINAL PUBLICATIONS

This study is based on the following original publications referred to in the text by their Roman numerals I-IV.

I Laasonen-Balk T, Viinamäki H, Kuikka J, Lehtonen J, Husso-Saastamoinen M, Mervaala E, Partanen J, Tiihonen J. Benzodiazepine receptor density in major depression. Nord J Psychiatry 54:361-363, 2000.

II Laasonen-Balk T, Kuikka J, Viinamäki H, Husso-Saastamoinen M, Lehtonen J, Tiihonen J. Striatal dopamine transporter density in major depression. Psychopharmacology 144:282-285, 1999.

III Laasonen-Balk T, Viinamäki H, Kuikka J, Husso-Saastamoinen M, Lehtonen J, Halonen P, Tiihonen J. Cluster C personality disorder has no independent effect on striatal dopamine transporter densities in major depression. Psychopharmacology 155:113-114, 2001.

IV Laasonen-Balk T, Viinamäki H, Kuikka JT, Husso-Saastamoinen M, Lehtonen J, Tiihonen J. $^{123}$I-β-CIT binding and recovery from depression: A six-month follow-up study. Eur Arch Psychiatry Clin Neurosci 254:152-155, 2004.

**CONTENTS**

# 1 INTRODUCTION

Depression is a common and important psychiatric disorder worldwide. In Finland it has become the most common mental disorder leading to disability pensions (Finnish Centre for Pensions and the Social Insurance Institution 2003). The etiology of depression is a combination of neurobiological and psychosocial factors. As early as 1937, Papez published his classic and widely cited article "A proposed mechanism of emotion" (Papez 1937). In this article he proposed that the hypothalamus, cingulus and hippocampus have a central role in the corticothalamic mechanism of emotion. There are two major hypotheses concerning the etiology of depression: the hypothesis of monoaminergic neurotransmission deficiency and the hypothesis of neurotrophic effects.

Brain imaging study techniques began to develop in the 1960s. The first techniques made it possible to examine the anatomical structures of the brain. Later, due to the development of these techniques it became possible to study the functional anatomy and metabolic changes of the brain. In the 1990s, dubbed the "Decade of the Brain", many remarkable findings were made from functional brain imaging studies. In the last decade it became possible to investigate neurotransmitters and transporters of the brain *in vivo* instead of *post mortem*, which was the main technique in the 1980s. The results of research using functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) have led to better understanding of the etiology and neurochemistry of mental illness.

The mechanism of action of antidepressant medication has become increasingly familiar due to better understanding of neurobiology and the findings of brain imaging studies. Improved knowledge of how antidepressants act at the neuronal level allows us to treat our patients more safely and effectively and to combine these drugs with each other.

# 2 REVIEW OF THE LITERATURE

## 2.1. Epidemiology and diagnostics of major depression

Major depression is a common psychiatric disorder. The reported prevalence of depressive disorders and depressive episodes depends on the subjects and the methods used. The lifetime prevalence of major depression has been found to vary between 9-26% among women and 5-12% among men (American Psychiatric Association 1987). Narrow et al. (2002) published revised prevalence estimates of mental disorders in the United States by selecting the lower estimate of the Epidemiologic Catchment Area study (ECA) (n = 20 861) and National Comorbidity Survey (NCS) (n = 8 098) for each diagnostic category, accounting for comorbidity, and combining categories. The revised one-year prevalence rate was 5.1% for any mood disorders, 4.5% for major depressive episodes, 4.0% for unipolar major depression and 1.6% for dysthymia. In Finland, according to the Terveys 2000 study (n = 8 028) (Terveys ja toimintakyky Suomessa 2002), 5% of study subjects had had major depression in the preceeding 12 months. Furthermore, the same study demonstrated that episodes of depression occur more often in women (7%) than in men (4%).

According to the Outcome of Depression International Network (ODIN) study, the prevalence of depressive disorders in Europe differed widely across the study sites (Ayuso-Mateos et al. 2001). The cities and rural areas that participated in this study were Liverpool and the Welsh Vale of Clwyd (United Kingdom), Dublin and the county of Laois (Ireland), Oslo and the district of Rakkestad (Norway), Santander (Spain), and Turku and the three municipalities of Marttila, Koski TL and Tarvasjoki (Finland). The total sample size in this study was 8 764, while the overall prevalence of depressive disorder was 8.6% and the prevalence in women and men, respectively, was 10.1% and 6.6%.The highest prevalence of depressive disorder was recorded in Liverpool (17.1%) and the lowest in Santander (2.6%). Rural communities showed a lower prevalence of depressive episodes than urban areas in Finland, Ireland and the United Kingdom, but the prevalence of depressive disorders was higher in rural communities than urban areas in both Norway and Finland. The

ODIN prevalence of depressive disorders in Finland was 5.9% in urban areas and 6.5% in rural areas. In Finland the prevalence differed between sexes, varying in women from 7.4% (rural) to 8.4% (urban) and in men from 3.3% (urban) to 5.6% (rural).

At the end of 2002, recipients of a disability pension due to mental disorders among residents of Finland totalled over 104 000, which was 41% of all disability pensions. Each year, over 4000 people become unable to work because of depression. In 2002, 34% of all disability pensions in Finland were due to mental disorders and 19% due to mood disorders (Finnish Centre for Pensions and the Social Insurance Institution 2003). In that year, mood disorders accounted for 2 163 335 lost working days at a cost of 86 million euros, which was 14% of all daily compensation costs (Kansaneläkelaitoksen julkaisuja 2003). As many as 288 000 persons (5.6% of the Finnish population) obtained reimbursement from the Social Insurance Institution in 2002 for antidepressant medications (Kansaneläkelaitos 2003). This is the same level as the prevalence of major depression in Finland (Terveys ja toimintakyky Suomessa 2002). Thus, major depression is a very important disorder when considered from the point of view of national health. It causes significant costs and a lot of human suffering.

### 2.1.1. The DSM-III-R criteria for major depression

The criteria for major depression according to American Psychiatric Association (1987) are listed below.

Diagnostic criteria for Major Depressive Episode

Note: A "Major depressive syndrome" is defined as criterion A below.

A. At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition,

mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations.)

(1) Depressed mood (or can be irritable mood in children and adolescent) most of the day, nearly every day, as indicated either by subjective account or observation by other.
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time).
(3) Significant weight loss or weight gain when not dieting (e.g., more than 5% of body weight in a month), or decrease or increase in appetite nearly every day (in children, consider failure to make expected weight gains).
(4) Insomnia or hypersomnia nearly every day.
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
(6) Fatique or loss of energy nearly every day.
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. (1) It cannot be established that an organic factor initiated and maintained the disturbance.
(2) The disturbance is not a normal reaction to the death of a loved one (Uncomplicated Bereavement).

Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major Depression.

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).

D. Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.

Major Depressive Episode codes: fifth-digit code numbers and criteria for severity of current state of Bipolar Disorder, Depressed, or Major Depression:

1- Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.
2- Moderate: Symptoms or functional impairment between "mild" and "severe".
3- Severe, without Psychotic Features: Several symptoms in excess of those required to make the diagnosis, and symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.
4- With Psychotic Features: Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent. Mood-congruent psychotic features: Delusions or hallucinations whose content are entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Mood-incongruent psychotic features: Delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Included here are such symptoms as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control.

5- In Partial Remission: Intermediate between "In full Remission" and "Mild", and no previous Dysthymia. (If Major Depression Episode was superimposed on Dysthymia, the diagnosis of Dysthymia alone is given once the full criteria for a Major Depressive Episode are no longer met.)
6- In full Remission: During the part six months no significant signs or symptoms of the disturbance.
0- Unspecified.

Specify chronic if current episode has lasted two consecutive years without a period of two months or longer during which there were no significant depressive symptoms.

Specify if current episode is Melancholic Type.

Diagnostic criteria for Major Depression

Major Depression, Single Episode

A. A single Major Depressive Episode.
B. Has never had a Manic Episode or an unequivocal Hypomanic Episode.

Specify if seasonal pattern.

Major Depression, Recurrent

A. Two or more Major Depressive Episodes, each separated by at least two months of return to more or less usual functioning. (If there has been a previous Major Depressive Episode, the current episode of depression need not meet the full criteria for a Major Depressive Episode.)
B. Has never had a Manic Episode or an unequivocal Hypomanic Episode.

Specify if seasonal pattern. (American Psychiatric Association 1987)

### 2.1.2. The severity of depression according to the HRSD-, BDI- and MADRS - scales

Because physicians may have problems in identifying depression, it is useful to use scales and questionnaires to assess the severity of depression. The clinician-rated Hamilton Rating Scale for Depression (HRSD) and self-rated Beck Depression Inventory (BDI) have been used in research into depression over the past four decades (Hamilton 1960, Beck et al. 1961). The Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician-rated scale and has been used in depression research for over 20 years (Montgomery and Åsberg 1979).

The cut-off points are dependent on the sample and the sensitivity and specificity have to be noted. Sensitivity signifies the test's ability to identify true cases and specifity is the test's reliability in identifying non-cases. In general, if the test is very sensitive it is often less specific. The reliability of a measure is the precision with which it can separate one subject from another. Discrimination, consistency and repeatability are included in the reliability. The validity of a measure is the degree to which the diagnosis, rating, category, or score it gives is description of the true state of nature. (Blacker and Endicott 2000)

There are four versions of the HRSD. The initial scale included 17 items measuring symptoms of depression as well as anxiety and hypochondriasis. The items consist of: 1) Depressed mood; 2) Guilt; 3) Suicide; 4) Insomnia, initial; 5) Insomnia, middle; 6) Insomnia, delayed; 7) Work and interests; 8) Retardation; 9) Agitation; 10) Anxiety, psychic; 11) Anxiety, somatic; 12) Somatic symptoms, gastrointestinal; 13) Somatic symptoms, general; 14) Genital symptoms; 15) Hypochondriasis; 16) Loss of weight; and 17) Insight. The 21-item version of the same scale included four additional items: diurnal variation, depersonalization and derealization, paranoid symptoms and obsessive-compulsive symptoms. The 24-item version also included items that measure helplessness, hopelessness and worthlessness. The six-item version of the HRSD only measures depressed mood, guilt, work, retardation, anxiety and somatic symptoms. The 17-, 21- and 24-item versions of the HRSD have been widely used in clinical trials (O'Sullivan et al., 1997). The 17-item HRSD score ranges from 0-52 (Hamilton 1960). The following cut-off

scores of the HRSD-17 are often seen when depressed patients are studied: 0-7 = no depression; 8-14 = mild depression; over 15 = moderate or severe depression. There have been few cut-off point studies of the HRSD (Viinamäki et al. 2005).

The BDI was derived from clinical observations about the attitudes and symptoms displayed by depressed psychiatric patients. The clinical observations were consolidated systematically into 21 symptoms and attitudes that could be rated from 0 to 3 in terms of intensity. The 21 symptoms and attitudes were: 1) Mood; 2) Pessimism; 3) Sense of failure; 4) Lack of satisfaction; 5) Guilt feelings; 6) Sense of punishment; 7) Self-dislike; 8) Self-accusation; 9) Suicidal wishes; 10) Crying; 11) Irritability; 12) Social withdrawal; 13) Indecisiveness; 14) Distortion of body image; 15) Work inhibition; 16) Sleep disturbance; 17) Fatigability; 18) Loss of appetite; 19) Weight loss; 20) Somatic preoccupation; and 21) Loss of libido. The BDI was initially designed to be administered by trained interviewers, but it is most often self-administered. The cut-off point in accordance with Beck is 12/13 when detecting depression among psychiatric patients, while a cut-off point of 9/10 should be used among medical patients (Beck and Beamesderfer 1974). Viinamäki et al. (2004) suggested that with a cut-off point of 14/15 the BDI-21 can be used to indicate the presence of a major depressive episode, regardless of the phase of the major depression. The Center for Cognitive Therapy has distributed the following guidelines for BDI cut-off scores with patients diagnosed as having an affective disorder: none or minimal depression is < 10; mild or moderate depression is 10-18; moderate to severe depression is 19-29; and severe depression is 30-63 (Beck et al. 1988).

The MADRS consists of the 10 items that include all core symptoms of depressive illness. The items are: 1) Apparent sadness; 2) Reported sadness; 3) Inner tension; 4) Reduced sleep; 5) Reduced appetite; 6) Concentration difficulties; 7) Lassitude; 8) Inability to feel; 9) Pessimistic thoughts; and 10) Suicidal thoughts (Montgomery and Åsberg 1979). The usual cut-off scores of the MADRS when studying depressive patients are: 0-8 = no depression; 9-17 = mild depression; 18-34 = moderate depression; and over 35 = severe depression (Müller et al. 2000).

### 2.1.3. Verifying the diagnosis by using SCID

Because the psychiatric diagnosis is difficult and possibly unreliable, structured and semistructured diagnostic interviews were designed to reduce information variance and thus increase reliability. The reliability of a diagnostic interview is influenced by many factors, such as the questions included and how well they are understood by the patient, the conditions under which the interview is administered, the training of the interviewers, how well the interviewer knew the patient before and the types of disorders covered. The validity of a diagnostic interview depends on the existence of a gold standard diagnosis with which it can be compared. Unfortunately, no gold standard for psychiatric diagnosis exists. (Skodol and Bender 2000)

The SCID is a semistructured clinical interview for making the major axis I DSM diagnosis. Diagnoses included in SCID modules are psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, adjustment disorders and personality disorders in the SCID II version. The SCID guides the clinician in testing diagnostic hypotheses as the interview is conducted. The output of the SCID is a record of the presence or absence of each of the disorders being considered for the current episode or for the lifetime occurrence. (Spitzer et al. 1992) There are also some other structured clinical interviews like the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and the Composite International Diagnostic Interview (CIDI) (Skodol and Bender 2000).

## 2.2. Neurochemistry of depression

The first major hypothesis on the pathophysiology of depression was that depression is caused by a deficiency of monoamine neurotransmitters. New information has been found about the effects of neurotrophins on mood disorders during the past decade (Castrén 2004). The neurotrophic hypothesis proposes that stress leads to neuronal atrophy, death and reduced neurogenesis, particularly in the hippocampus, by modulating hippocampal synaptic plasticity and elevating basal synaptic transmission. According to the hypothesis, antidepressants produce a stimulation of intracellular signaling pathways that leads to an up-regulation of cAMP response

element binding protein (CREB) and increased expression of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) (Popoli et al. 2002). CREB regulates the proliferation and the survival of the newborn neurons in the hippocampus (Nakagawa et al. 2002). Antidepressants and mood-stabilizing drugs act as a double-active mechanism, which means that they have an influence on neurotransmitter function and they can modulate signal transduction pathways and neurotrophic factor gene expression (Duman et al. 1997). Neurotrophic changes caused by antidepressants are not rapid, because the morphological changes probably take time to develop and mature, and this might partly explain the delay in the development of the clinical response to antidepressant medication.

There is considerable overlap between different neurotransmitter pathways. The synthesis, metabolism and neurotransmission of monoamines and other neurotransmitters have a direct or indirect influence on each other (see Figure 1). (Baraban and Coyle 1995, Paul and Skolnick 2003)

There is also considerable overlap between those intracellular pathways that mediate neuronal depolarization and neural plasticity and those that control cell survival. Learning, memory, stress, other behavioural experiences and psychotropic drugs activate the appropriate neural circuit, which includes the neurotrophic factors and neurotransmitter-coupled signal transduction cascades as well as other modulators and their cascades. These cascades intersect at convergent points and induce molecular and cellular adaptations that underlie neural plasticity. These pathways may result in increased neural plasticity and cell survival, but in the case of failure they can lead to atrophy and death of the neurons. (Duman et al. 2000)

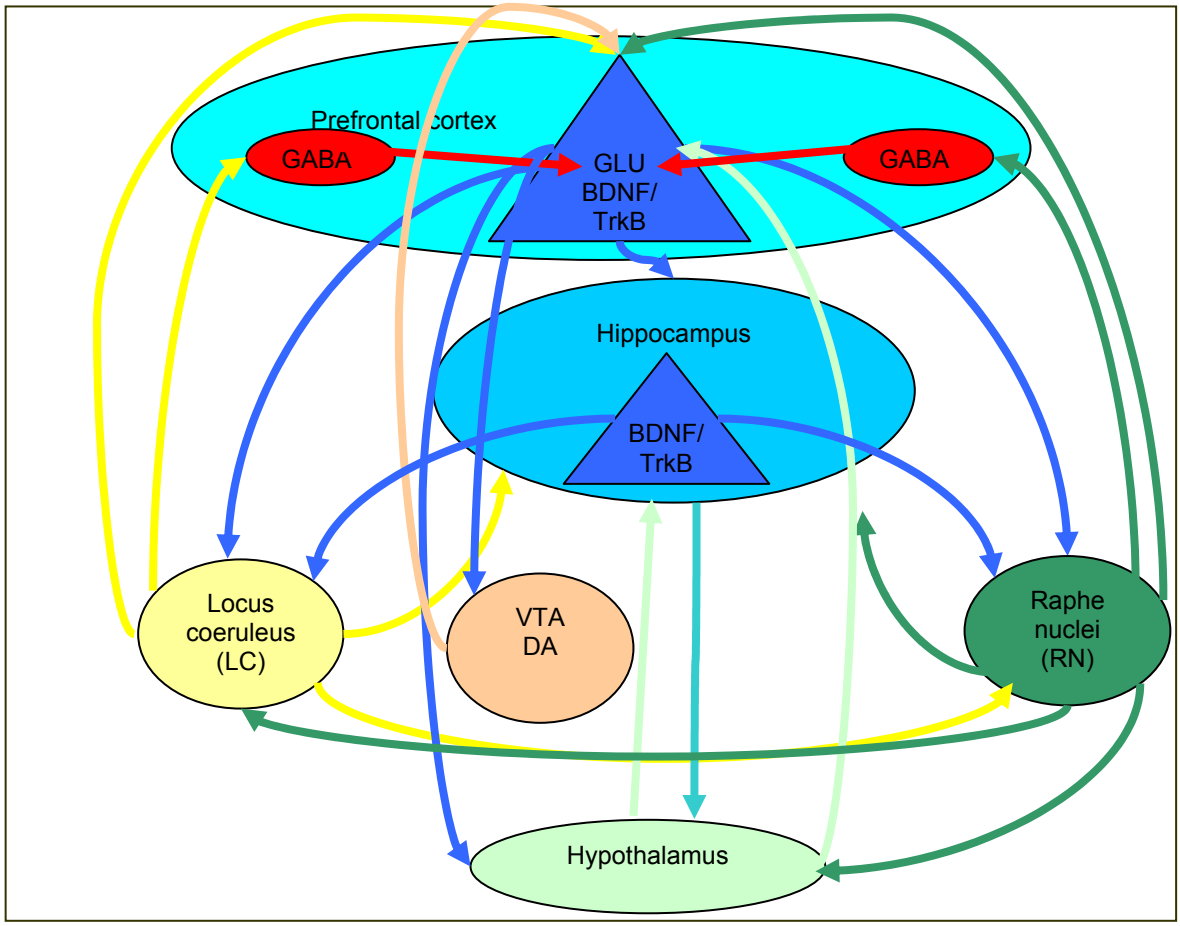


Figure 1. Schematic diagram of the neural circuitry of relevance to the interaction of GABAergic, serotonergic, noradrenergic, dopaminergic and glutamatergic neurotransmission and BDNF/TrkB modulatory presynaptic connections on glutamatergic pyramidal cells in the prefrontal cortex and hippocampus. VTA = ventral tegmental area. GABAergic interneurons and the apical dentrites of glutamatergic pyramidal neurons of prefrontal cortex are modulated by the noradrenergic projections from the locus coereleus (LC) and by the serotonergic projections from the raphe nuclei (RN). The activation of glutamatergic pyramidal neurons of the prefrontal cortex modulates glutamatergic neuronal activity in the hippocampus and has glutamatergic feedback connections both directly to the LC and the RN. There are reciprocal modulatory projections between the LC and RN. Stimulation of both synaptic NMDA receptors and AMPA receptors can activate the phosphorylation of CREB and enhance the expression of BDNF and TrkB. Increased expression and release of BDNF and activation of TrkB promote the function, sprouting and regrowth of 5-HT and NA containing neurons (Altar 1999). Activation of glutamate receptors stimulates the $Ca^{2+}$ -calmodulin- nitric oxide (NO) cascade and leads to the synthesis and release of NO. NO may be able to stimulate the release of DA and NA, depending on NMDA receptor stimulation. The mesolimbic DA system originates from the VTA and projects to the limbic striatum, including the nucleus accumbens (not shown), to the amygdaloid body (not shown) and to other limbic areas, such as the prefrontal cortex. DA neurons in the VTA receive direct excitative glutamatergic innervation (via both ionotropic and metabotropic receptors) from the prefrontal cortex. (Modified from Paul and Skolnick 2003)

### 2.2.1. Monoamine hypothesis of depression

According to the monoamine hypothesis of depression, depression is due to the reduced availability of monoamine neurotransmitters, dopamine (DA), serotonin (5-hydroxytryptamine (5-HT) and noradrenaline (NA, called also norepinephrine (NE)). Ascending and descending tracts of DA, 5-HT and NA systems project to the limbic and prefrontal cortex as well as to the striatum and other cortical areas. The cingulate gyrus has extensive projections to the basal, medial, and lateral surfaces of the cerebral hemispheres. The monoamine receptors are distributed in the cortical regions, the striatum and the limbic system. This network is involved in modulation and feedback mechanisms among the brain regions. (Trivedi and Husain 1997)

The presynaptic monoaminergic neurons have reuptake pumps called transporters that are selective for each monoamine. They are called the DA transporter (DAT), serotonin transporter (SERT) and norepinephrine transporter (NET). In the normal state there is a balance between monoamine synthesis, release and neurotransmission. According to the monoamine hypothesis, in the case of depression the monoamine neurotransmitters are depleted, causing neurotransmitter deficiency. DA and NA can be eliminated by enzymes in the neuron. The principal destructive enzymes are monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). The action of DA and NA can be terminated not only by enzymes, but also by DAT and NET. Serotonin can also be eliminated by the MAO enzyme and converted into an inactive metabolite. The SERT is analogous to the DAT and NET. The transporter prevents monoamine from acting on the synapse without destroying it. It takes monoamine back into the cell from the synaptic cleft and off the synaptic receptors, stopping its synaptic actions. Inside the presynaptic nerve terminal, monoamine can be stored again for reuse when another nerve impulse arrives or it can be metabolized by enzymes. (Stahl 2001)

The neurotransmitter receptor hypothesis of depression posits that the depletion of neurotransmitter causes compensatory up-regulation of postsynaptic neuroreceptors, which may prevent normal neurotransmission by absorbing neurotransmitters from the synaptic cleft and thus causing a depletion of monoamine neurotransmitter in there. The monoamine hypothesis of gene action in depression

suggests that depression may be caused by a deficiency in signal transduction in the postsynaptic neuron, although there are normal amounts of neurotransmitters and receptors. The transduction of the signal from the neurotransmitter receptor is somehow damaged. The second messenger systems leading to the formation of intracellular transcription factors that control gene regulation could be the site of inadequate functioning of monoamine systems. It has been proposed that the site of a defect in signal transduction from monoamine receptors is the target gene for brain-derived neurotrophic factor (BDNF). (Duman et al. 1997, Stahl 2001)

There is a large overlap between the roles played by neurotrophins and monoamines in the regulation of brain function. Normally, BDNF enhances the growth of serotonin and NA neurons and protects them from neurotoxic damage. Restraint or psychosocial stress decreases the expression of BDNF. This may lead to the atrophy or even death of vulnerable neurons in the hippocampus. Increased glucocorticoid levels or neuronal insults such as hypoxia-ischemia, hypoglycemia, neurotoxins or viral infections could cause direct neuronal damage or might make neurons increasingly sensitive to stress. Such changes could lead to depression at later times or, if severe enough, could immediately precipitate a depressive episode. (More about BDNF in 2.2.3.) (Duman et al. 1997, Stahl 2001)

#### 2.2.1.1. Dopamine

Most brain dopamine is situated in the basal ganglia, the substantia nigra and the ventral tegmental area (VTA). Dopamine synthesis originates from the amino acid precursor tyrosine, which must be transported into the dopamine neuron. In the neuron, tyrosine is converted from L-tyrosine into L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. DOPA is converted to dopamine by L-aromatic amino acid decarboxylase. Newly synthesized dopamine is stored in a functional pool, which is preferentially released on nerve stimulation by a calcium-dependent process. Dopamine release from the nerve terminal is regulated by presynaptic release-modulating autoreceptors. Dopamine agonists inhibit and antagonists increase the evoked release of dopamine. Released dopamine can

stimulate autoreceptors, and this stimulation initiates a negative feedback effect on dopamine synthesis to further reduce the release of dopamine. (Cooper et al. 1996)

In striatal dopamine-nerve terminals there are high-affinity dopamine uptake sites that are important in terminating transmitter action and in maintaining transmitter homeostasis. The DAT is a component of the functioning dopamine nerve terminal and its role is to pump extracellular dopamine back into the nerve terminal from the synaptic cleft. After reuptake by the nerve terminal, released dopamine is converted to dihydroxyphenylacetic acid (DOPAC) by intraneuronal monoamine oxidase (MAO). Released dopamine is also converted to homovanillic acid (HVA) by catechol-O-methyltransferase (COMT) and MAO. The primary metabolites of dopamine in the CNS are HVA, DOPAC and a small amount of 3-methoxytyramine (3-MT). Increased impulse flow in the mesolimbic (originates in the VTA) or nigrostriatal (originates in the substantia nigra) dopamine system does lead to both an enhancement in dopamine synthesis and turnover and a frequency-dependent increase in the accumulation of dopamine metabolites in the striatum and olfactory tubercle. (Cooper et al. 1996)

Dopamine inhibits neuronal activity by direct action, but indirectly produces a positive response by preventing inhibitory neurons. Dopamine is both a transmitter and a precursor for the synthesis of adrenaline and noradrenaline. Stimulation of postsynaptic receptors by dopamine is a key event in the synaptic transmission process. Dopamine can activate at least five major subtypes of dopamine receptors (Wilcox et al. 1998). Administration of L-DOPA increases dopamine synthesis and synaptic dopamine concentrations, and thereby activates postsynaptic receptors. Dopamine receptor agonists have similar effects (e.g. bromocryptine). (Wagner and Wong 1990)

Caligiuri and Ellwanger (2000) showed that motor slowing was related to severe depression and it may be a characteristic trait in depression. Their findings suggest that bipolar depression patients exhibit motor retardation that more closely resembles parkinsonian bradykinesia and may due to a similar dysfunction in the basal ganglia. Sachdev and Aniss (1994) have earlier suggested that dopamine may be involved in the pathogenesis of psychomotor slowing in melancholic depression. Ebert et al. (1996) suggested that lower levels of striatal dopamine are released in depressed

patients with psychomotor retardation, and that an improvement in depression may lead to an increase in striatal dopamine turnover. Altered dopamine transporter binding could also be related to the presence of mood changes in depression. Tiihonen et al. (1996) found that the intake of 5-HT re-uptake inhibitor citalopram decreased [$^{11}$C]raclopride binding, which may reflect increased dopamine release in the striatum. This suggests a functional interaction of brain dopaminergic and serotonergic systems, and some of the clinical effects of 5-HT re-uptake inhibitors may be mediated by their indirect modulating effects on dopaminergic transmission.

#### 2.2.1.2. Serotonin

Serotonin producing neurons project from the midbrain or the raphe nuclei in the brain stem to neurons in diverse regions of the central nervous system (Nemeroff 1998).

Serotonin, 5-hydroxytryptamine (5-HT), is synthetized from tryptophan first to 5-hydroxytrytophan (5-HTP) by the enzyme tryptophan hydroxylase. 5-HTP is then converted to 5-HT by amino acid decarboxylase. 5-HT is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by MAO and aldehyde dehydrogenase. 5-HIAA is the main metabolite of 5-HT. There are high-affinity serotonin uptake sites in serotonin nerve terminals. These uptake sites play an important role in terminating transmitter action and in maintaining transmitter homeostasis. Depending on the concentration gradient, a plasma membrane carrier is capable of transporting serotonin in either direction. (Cooper et al. 1996) Once taken up into the presynaptic neuron by serotonin transporter protein (SERT), 5-HT may be degraded to 5-HIAA or it can be repackaged into secretory vesicles via the vesicular monoamine transporter (Owens and Nemeroff 1998).

5-HT receptors belong to the G-protein-coupled receptor (GPCR) superfamily, with at least 14 distinct members, and represent one of the most complex families of neurotransmitter receptors (Hoyer et al. 2002). 5-HT receptors have two major signal transduction pathways: 1) direct regulation of ion channels and 2) a multistep enzyme-mediated pathway. Both pathways need a guanine nucleotide triphosphate (GTP) - binding protein (G protein) to link the receptor to the effector molecule.

Inhibitory effects of 5-HT are mediated by 5-$HT_1$ receptors linked to the opening $K^+$ channels or to the closing of $Ca^{2+}$ channels via G proteins. The 5-$HT_1$ receptor family also causes the inhibition of the adenylate cyclase. 5-$HT_{1A}$ receptors have been proposed to play a role in modulating anxiety-related behaviours (Hoyer et al. 2002). 5-$HT_{1B}$ receptors are expressed in the basal ganglia, striatum and frontal cortex and they may act as a terminal heteroreceptor controlling the release of other neurotransmitters (Hoyer et al. 2002). The facilitatory effects of 5-HT are mediated by 5-$HT_2$, 5-$HT_4$ and 5-$HT_7$ (Cooper et al. 1996). 5-$HT_{2A}$ receptors are located centrally in the cortex, claustrum and basal ganglia and activation of this receptor subtype can stimulate hormone secretion, e.g. ACTH, corticosterone, oxytocin, renin and prolactin (Hoyer et al. 2002). It is suggested that the combination of dopamine $D_2$ and 5-$HT_{2A}$ receptor antagonism may best explain the antipsychotic activity of drugs such as clozapine, olanzapine and seroquel (Hoyer et al. 2002). 5-$HT_3$ receptors are primarily present in nerve terminals, where they regulate the release of neurotransmitters. They regulate the gating of cations and thus mediate the rapid and transient depolarization that occurs following receptor activation (Cooper et al. 1996). 5-$HT_4$ receptors in the CNS appear to modulate neurotransmitter (acetylcholine, dopamine, serotonin and GABA) release and enchance synaptic transmission (Hoyer et al. 2002). The distribution of 5-$HT_7$ binding sites in the limbic system and thalamocortical regions suggests a possible role in the pathohysiology of affective disorders (Hoyer et al. 2002).

Delgado et al. (1990) found that acute plasma tryptophan depletion led to a clinically significant return to depressive symptoms in 14 (67%) of 21 patients who had recently remitted from depression after successful treatment with antidepressant medication. Later, Delgado et al. (1994) found that tryptophan depletion did not rapidly worsen depression, arguing that serotonin function is not linearly related to the level of depression. They also suggested that if reduced serotonin function does cause depression, then it is either as predisposing factor or due to a presynaptic deficit in the utilization of serotonin. Other experiments with patients in clinical remission and free of antidepressant medication have revealed that tryptophan depletion causes depressive symptoms (Smith et al. 1997, Moreno et al. 1999).

Later, Moreno et al. (2000) suggested that the mood response to tryptophan depletion may predict major depressive episodes in the future.

Sobczak et al. (2002) found that first-degree relatives of type I bipolar disorder patients showed a lowering of mood after acute tryptophan depletion. Booij et al. (2002) observed in their reanalysis study that acute tryptophan depletion induced depressive symptoms in 50% of recovered depressed patients, prior treated with selective serotonin reuptake inhibitor (SSRI). Rapid tryptophan depletion leads to lower 5-HT levels in the CNS and this may increase impulsiveness, even in normal individuals (Walderhaug et al. 2002) and particularly in subjects with a family history of alcoholism (Crean et al. 2002).

Neumeister et al. (2002) found that the homozygous short (s) allele genotype of the serotonin transporter promoter gene region (5-HTTLPR) was associated with an increased risk of developing depressive symptoms during tryptophan depletion, irrespective of the family history of depression. Moreno et al. (2002) found that there was a significant association between the homozygous long (l) allele genotype of 5-HTTLPR and the depressive response to tryptophan depletion. Consistent with these findings of Moreno and coworkers (2002), Pierucci-Lagha et al. (2004) also reported that patients homozygous for the l allele at 5-HTTLPR had greater depressive symptoms after rapid tryptophan depletion than did heterozygous patients or those homozygous for the s allele. Caspi et al. (2003) found that individuals with one or two copies of the s allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms in relation to stressful life events than those who were homozygous for the l allele.

#### 2.2.1.3. Noradrenaline

The highest concentration of noradrenaline is usually found in the hypothalamus in the locus coeruleus, medulla oblongata and pons (Green et al. 1995). The synthesis of catecholamines (noradrenaline and adrenaline) begins with the amino acid precursor tyrosine. The sequence of enzymatic steps leads via DOPA to dopamine, which is a precursor for the synthesis of noradrenaline and adrenaline. Thus, inhibition of dopamine synthesis also inhibits noradrenaline and adrenaline synthesis.

N-methyl transferase and catechol-forming enzyme are the main enzymes that participate in the enzymatic conversion of dopamine to noradrenaline and adrenaline. The feedback regulation and other processes linked to neuronal activity control noradrenaline synthesis. Noradrenaline is bound and stored in special vesicles in sympathetic nerve terminals and chromaffin cells and is safe from monoamine oxidase (MAO). The vesicles can release the transmitter upon the appropriate physiological stimulus. An influx of $Ca^{2+}$ may be the main stimulus responsible for the mobilization of noradrenaline. Presynaptic autoreceptors modulate noradrenaline release and reuptake carrier protein its reuptake. The noradrenaline transporter (NET) is an $Na^{+}/Cl^{-}$-dependent neurotransmitter transporter that takes up transmitter from the synaptic cleft. The main metabolite of noradrenaline is vanilylmandelic acid (VMA), but it is rarely found in the brain. The principle metabolite found in the brain is 3-methoxy-4-hydroxy-phenethyleneglycol (MHPG). (Cooper et al. 1996)

Klimek et al. (1997) recorded decreased binding of [$^{3}$H]nisoxetine to NETs in the locus coeruleus in major depression. They assumed that this may reflect a compensatory downregulation of this transporter protein as response to an insufficient availability of noradrenaline at the synapse. Klimek et al. (1999) observed no significant differences in binding to $\alpha$-2, $\beta$-1, or $\beta$-2 adrenoceptors in the frontal cortex and hippocampus from major depression patients compared to healthy controls. However, the changes in second messenger systems or the affinity of noradrenaline for these receptors may be altered in depression.

### 2.2.2. GABA and benzodiazepine receptors

In the mammalian central nervous system (CNS) there are two general classes of amino acids: 1) exitatory amino acids (glutamic acid, aspartic acid, cysteic acid, and homocysteic acid) and 2) inhibitory amino acids (gamma amino butyric acid (GABA), glycine, taurine, and $\beta$-alanine). The former depolarize and the latter hyperpolarize neurons (Cooper et al. 1996).

GABA was first synthesized in 1883, but not until 1950 was it identified as a normal constituent of the mammalian CNS. In mammals, the brain and spinal cord contain high concentrations of GABA. GABA functions as an inhibitory transmitter in

the brain, and the highest concentration of GABA occurs in the globus pallidus and the substantia nigra. The GABA receptor usually refers to a GABA recognition site on pre- and postsynaptic membranes that, when coupled with GABA or an appropriate agonist, causes a shift in membrane permeability to inorganic ions, primarily chloride. This change in chloride permeability leads to hyperpolarization of the receptive neuron in the case of postsynaptic inhibition or depolarization in the case of pre-synaptic inhibition. In humans there are two major types of GABA receptors: the $GABA_A$ receptor and the $GABA_B$ receptor. (Cooper et al. 1996)

The $GABA_A$ receptor is a multi-subunit receptor-channel complex that can be allosterically modulated by two important classes of drugs, the benzodiazepines and the barbiturates. The $GABA_A$ receptor complex has both benzodiazepine receptor and $GABA_A$ receptor parts, and it is also called the $GABA_A$-benzodiazepine receptor. Activation of the $GABA_A$ receptor by GABA agonists leads to opening of the chloride channel. Chloride anions flow in through the channel and inhibit the firing of the neurons by causing hyperpolarization. Benzodiazepines enhance the frequency of channel opening without appreciably altering the channel conductance or duration of opening. Barbiturates slightly decrease the opening frequency and prolong the duration of opening. The $GABA_A$ receptor has a structure containing two $\alpha$ and $\beta$ subunits and a single $\gamma$ subunit to form an intrinsic Cl-ion channel. The $\gamma$-subunit is necessary for the potentiation of GABA responses by benzodiazepines. (Cooper et al. 1996, Chang et al. 2003)

$GABA_B$ receptor activation also plays a role in attenuating the release of amines, excitatory amino acids, neuropeptides and hormones. The $GABA_B$ receptors seem to be coupled to $Ca^{2+}$ or $K^+$ channels via second messenger systems. The inhibitory action of $GABA_B$ receptor activation appears to be mediated through either increases in potassium conductance or decreases in calcium conductance. Unlike the $GABA_A$ receptor, the $GABA_B$ receptor is not modified by benzodiazepines or barbiturates. (Cooper et al. 1996)

The GABA-benzodiazepine receptor complex is probably involved in the pathogenesis of anxiety, a condition that is commonly associated with depression. Depressed patients demonstrated a highly significant (52%) reduction in occipital cortex GABA levels compared with healthy subjects in a magnetic resonance

spectroscopy study (Sanacora et al. 1999). Sanacora et al. (2002) demonstrated a 34 % increase in occipital cortex GABA concentrations after treatment of SSRI in a group of depressed patients. This finding suggests that normalization of abnormally low cortical GABA concentrations may provide a common mechanism in the treatment of major depression.

### 2.2.3. Neurotrophic hypothesis of depression

Neurotrophins, such as brain-derived neurotrophic factor (BDNF) found in the dendrites of CA3 pyramidal neurons in the hippocampus, regulate neuronal development and survival, and control synaptic function and plasticity. Neuronal activity regulates the transcription of the BDNF gene, the transport of BDNF mRNA and protein into dendrites and the secretion of BDNF protein. Further, there is also evidence that the cell surface expression and ligand-induced endocytosis of the BDNF receptor tyrosine kinase, TrkB, are regulated by neuronal activity that simultaneously induces $Ca^{2+}$ influx. Neurotransmitter glutamate can induce neurotrophin secretion in the hippocampal neurons. There is a suggestion that activity-dependent secretion of BDNF is important for human hippocampal functions such as learning and memory. (Huang and Reichardt 2001, Lu 2003) Eisch et al. (2003) suggested that BDNF might be prodepressive in another brain circuit implicated in depression: the ventral tegmental area-nucleus accumbens pathway.

Antidepressant treatment induces the activation of BDNF receptor TrkB in the rodent hippocampus and prefrontal and anterior cingulate cortex. Antidepressants acutely increase TrkB signalling and BDNF release, which are both required and necessary for antidepressant-like behavioural effects. (Saarelainen et al. 2003)

A postmortem human study showed that antidepressant medications increase hippocampal BDNF immunoreactivity (Chen et al. 2001). Shimizu et al. (2003) found significantly lower serum BDNF levels in depressed patients without antidepressants compared to both drug-treated patients and healthy controls. They also measured the serum BDNF levels of four drug-naive depressed patients both before and after antidepressant treatment. They found that after eight weeks of antidepressant treatment, the reduced BDNF levels of three patients recovered to the normal levels.

Antidepressants have been shown to have a preventative effect on the atrophic changes produced by stress in the rat hippocampus (Czéh et al. 2001, Norrholm et al. 2001). A single intrahippocampal injection of BDNF produces antidepressant-like behavioural effects within three days and lasts at least ten days (Shirayama et al. 2002).

ECT induces mossy fibre sprouting in the rat hippocampus (Vaidya et al. 1999, Lamont et al. 2001). Michael et al. (2003) observed a significant increase in N-acetylaspartate (NAA) concentrations after successful ECT treatment in depressed patients. They suggested that this finding may indicate a probable neurotrophic effect of ECT.

Early maternal deprivation and chronic stress can reduce BDNF mRNA levels and NMDA receptor subunits in the rodent hippocampus. It is proposed that this can cause a reduction in cellular plasticity and permanent alterations in brain function, which might lead to an increased vulnerability to psychiatric disorders such as depression and schizophrenia. (Roceri et al. 2002)

#### 2.2.3.1. Glutamate receptors

Glutamate is the most abundant excitatory neurotransmitter in the brain. It is synthesised from glucose and glutamine in presynaptic nerve terminals. After synthesis, glutamate is stored in synaptic vesicles and released by a calcium-dependent exocytotic process. In the synaptic cleft glutamate acts on receptors. This synaptic action can be terminated by the reuptake of glutamate into the presynaptic nerve terminals (Cooper et al. 1996). Glutamate-containing neurons are found in the cortex and in subcortical regions such as the hippocampus, caudate nucleus, thalamic nuclei and the cerebellum (Paul and Skolnick 2003). In the hippocampus, glutamatergic synapses mediate major changes in synaptic plasticity induced by stress or antidepressant treatment. There are two main mediators of synaptic plasticity: an excitatory amino acid receptor, the NMDA (N-methyl-D-aspartate) receptor complex for glutamate, and $Ca^{2+}$/calmodulin-dependent protein kinase II (CaM kinase II). (Popoli et al. 2002)

There are different types of glutamate receptor, which have been pharmacologically classified as ionotropic (cation dependent gating) and metabotropic (adenylyl cyclase and phosphoinositide activity dependent gating). Ionotropic glutamate receptors include NMDA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) and kainate receptors. Metabotropic glutamate receptors include the receptors that are linked to G proteins and either activate phospholipase C or inhibit adenylate cyclase. (Belsham 2001)

The NMDA receptor is a complex molecular entity with a number of distinct binding sites for endogenous and exogenous ligands such as glutamate, polyamines and glysine. The glutamate and glysine sites must be occupied before the channel becomes permeable to cations. When the channel is open, $Na^+$ and $Ca^{2+}$ flow into the cell and $K^+$ flows in the opposite direction. Voltage-dependent $Mg^{2+}$ and voltage-independent $Zn^{2+}$ can block the channel as well as phencyclidine (PCP) and related noncompetitive antagonist (MK-801, ketamine). These agents act most effectively when the receptor is activated. A competitive antagonist at the NMDA site can also block the channel. (Cooper et al. 1996)

Stimulation of both synaptic NMDA and AMPA receptors activates CREB phosphorylation and BDNF gene expression. Activation of extrasynaptic NMDA receptors produces a dephosphorylation cascade of CREB that leads to CREB inactivation and the inactivation of BDNF. Antagonists of the NMDA receptor probably bind to the extrasynaptic NMDA receptors and in this way inhibit the CREB dephosphorylation cascade, which is the reason why they act paradoxically like antidepressants. (Paul and Skolnick 2003) Interactions occur with glutamatergic, monoaminergic and GABAergic neurotransmissions and neurotrophic functions, which are illustrated in Figure 1.

Plateled glutamate receptors may be supersensitive in depression, and depression may be associated with altered glutamatergic neurotransmission (Berk et al. 2001). Alterations in NMDA receptor function may be associated with the pathophysiology of four common psychiatric illnesses: schizophrenia, major depression, posttraumatic stress disorder, and alcoholism (Heresco-Levy and Javitt 1998). However, Meador-Woodruff et al. (2001) found no significant differences in

NMDA receptor subunit transcript and binding sites in the striatum between patients with depression, bipolar disorder and schizophrenia and healthy controls.

## 2.3. Neuroimaging

Neuroimaging can be divided into three branches: structural, chemical and functional neuroimaging. Magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) provide neurochemical information about the living human brain. Functional imaging also uses PET, SPECT and functional magnetic resonance imaging (fMRI). (Innis and Malison 1995, Sassi and Soares, 2003)

PET and SPECT techniques enable the observation of celebral blood flow (CBF), metabolism, and receptor and transporter binding. The usual isotopes in use are $O^{15}$, $C^{11}$ and $F^{18}$ with PET, and $I^{123}$, $Tc^{99m}$ and $Xe^{133}$ with SPECT. The specific radioligands bind to receptors and neurotransporters (Innis and Malison 1995). Some examples of the radioligands and their receptors are as follows. Iodine-123 labelled radioligands such as [$^{123}$I]3-iodo-6-methoxybenzamide ([$^{123}$I]IBZM) and [$^{123}$I]epidepride are used for imaging striatal and extrastriatal dopamine $D_2$ receptor sites in the human brain (Costa et al. 1990, Kuikka et al. 1997a). Technetium-99m labelled tropane, [$^{99m}$Tc]TRODAT-1, binds selectively to dopamine transporters in the brain (Kung et al. 1997). Iodine-123 or C-11 labelled 2β-carbomethoxy-3β-(4-iodophenyl)tropane ([$^{123}$I]β-CIT) was synthesized as a tracer for PET and SPECT studies of monoamine reuptake sites (Carroll et al. 1991, Neumeyer et al. 1991). The following paragraphs deal with some receptor-specific SPECT and PET studies using radiolabeled ligands.

### 2.3.1. [$^{123}$I]β-CIT SPECT studies

[$^{123}$I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([$^{123}$I]β-CIT) was independently synthesized and characterized as a SPECT tracer of monoamine reuptake sites by Neumeyer et al. (1991) and Carroll et al. (1991). [$^{123}$I]β-CIT was shown to be stable (98-99%) for at least 3 days (Zea-Ponce et al. 1995). As studies have demonstrated,

[$^{123}$I]β-CIT appears to be a suitable ligand for imaging dopamine and serotonin transporters in rodents (Boja et al. 1992, Fujita et al. 1996), monkeys (Innis et al. 1991, Laruelle et al. 1993) and humans (Brücke et al. 1993, Kuikka et al. 1993, 1995, Pirker et al. 2000). Because the affinity of [$^{123}$I]β-CIT for dopamine transporter is high, the concentration of endogenous dopamine does not affect β-CIT binding. Studies have shown that β-CIT binding in the striatum is almost exclusive to DATs, whereas binding in the hypothalamus and midbrain is mainly associated with SERTs (Innis et al. 1991, Laruelle et al. 1993, Staley et al. 1994, Pirker et al. 1995).

Kinetic studies have revealed a different time course of [$^{123}$I]β-CIT uptake in the striatum and in SERT-rich brain areas. Uptake in the striatum appears to reach a maximum approximately 16 h after injection and stabilizes for up to 24 h after injection. Peak uptake in the hypothalamus and midbrain occurs approximately 4 h after injection. Uptake in the occipital cortex and in the cerebellum, which are used as reference regions, peaks before 1 h after injection and stabilizes approximately 4 h after injection (Brücke et al. 1993, Laruelle et al. 1994). Bergström et al. (1995a,b) detected two metabolites of [$^{123}$I]β-CIT, one polar and the other lipophilic. The lipophilic metabolite may pass the blood-brain barrier and influence the quantitation of DAT and SERT.

Previous studies have shown the age-related decline of striatal [$^{123}$I]β-CIT binding to be 6.6% per decade (van Dyck et al. 2002a), and the age-associated decrease of [$^{123}$I]β-CIT binding in SERT-rich brain areas to be 3-4% per decade (Pirker et al. 2000, van Dyck et al. 2000). Staley et al. (2001) observed a higher striatal DAT and brainstem SERT availability in females than in males. Kuikka et al. (1997b) found a higher heterogeneity of DATs in the left side of the living human brain, and that females had a higher heterogeneity and a higher intercept in both the left and the right striatum than did males. This might be one reason why females have a finer control of motor behaviour than males.

Neumeister et al. (2000) suggested a reduced brain SERT availability in winter measured with [$^{123}$I]β-CIT SPECT. According to authors, this finding substantiates evidence of seasonal variations in brain serotonergic function. Using [$^{123}$I]β-CIT SPECT, Van Dyck et al. (2002b) observed no significant difference in striatal [$^{123}$I]β-

CIT binding between nine adult patients with attention deficit hyperactivity disorder (ADHD) and nine matched healthy controls.

### 2.3.2. Imaging of benzodiazepine receptors

The first SPECT study evaluating reduced regional iomazenil binding in panic disorder was carried out by Schlegel and colleges (1994). Iomazenil is a competitive $GABA_A$–benzodiazepine receptor antagonist, and it binds tightly to the benzodiazepine receptor complex. They found that panic patients had lower iomazenil uptake rates in the frontal, occipital and temporal cortex than epileptic patients, indicating the involvement of the benzodiazepine receptor complex in panic disorder. Kaschka et al. (1995) compared a group of nine patients with panic disorder and depression with a matched group of nine dysthymic patients without a previous or actual history of panic attacks or anxiety with iomazenil SPECT. At 2h after tracer injection they observed that the panic attack group had a significant decrease in the regional activity index in the right and left lateral inferior temporal lobes, the left medial inferior temporal lobe, and the right and left inferior frontal lobes. These findings may be due to either regional blood flow differences or benzodiazepine receptor effects. When the investigators compared the receptor binding phase (2h) values of the two groups by using the perfusion phase (10 min) as a covariate, only left lateral temporal hypoactivity remained significantly different between panic patients and controls. Kugaya et al. (2003a) found no altered cortical benzodiazepine binding in patients with depression compared with healthy controls measured with [$^{123}$I]iomazenil SPECT.

Kuikka et al. (1996) were the first to use [$^{123}$I]3-(5-cyclopropyl-1,2,4-oxadiazo-3-yl)-7-iodo-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine ([$^{123}$I]NNC 13-8241) for imaging benzodiazepine receptor sites in the living human brain. The benzodiazepine receptor binding of [$^{123}$I]NNC 13-8241 was significantly decreased in the left temporal pole among patients with generalized anxiety disorder (GAD) when compared with age- and sex-matched healthy controls (Tiihonen et al. 1997a).

There was decreased brain $GABA_A$–benzodiazepine receptor binding throughout the brain in patients with panic disorder compared with controls measured by [$^{11}$C]flumazenil PET (Malizia et al. 1998).

## 2.4. Neuroimaging in depression

Neuroimaging and neuropathological studies of depression have revealed both structural and functional abnormalities, particularly in the limbic system, the brainstem structures, the prefrontal cortex and in the striatum in patients with mood disorders (Drevets 2001, Sheline 2003).

A number of studies using magnetic resonance imaging (MRI) based measurements have reported reductions in the hippocampal volume in depressed patients (Sheline et al. 1996, 1999, 2003, Shah et al. 1998, Mervaala et al. 2000, Frodl et al. 2002, MacQueen et al. 2003, Campbell et al. 2004). Frodl et al. (2004) recently found that depressed patients with the homozygous long allele genotype of 5-HTTLPR had a significantly smaller hippocampal volume than controls with this genotype. Hippocampal volume loss has also been reported in patients with borderline personality disorder and early traumatization (Driessen et al. 2000), patients with posttraumatic stress disorder (Bremner et al. 1995) and in patients with early sexual or physical abuse (Bremner et al. 1997). Hippocampal volume loss in depression is probably mainly due to neuronal atrophy and only slightly, if at all, due to neuronal death (Lucassen et al. 2001). When imaging depressed patients and control subjects using PET during the verbal memory encoding task, Bremner et al. (2004) found that memory encoding resulted in greater activation in the hippocampus and anterior cingulate cortex among healthy subjects than among subjects with midlife major depression. This finding supported the hypothesis of hippocampal deficits in depression. The duration of depression, increased cortisol and the duration of combat exposure with posttraumatic stress disorder seem to cause a reduction in hippocampal volume (Sapolsky 1996).

Botteron et al. (2002) observed a volume reduction in the prefrontal cortex and Hastings et al. (2004) in the amygdala of depressed women, although reduced volumes of the amygdala have also been found in the early phases of schizophrenia

(Joyal et al. 2003). Ballmaier et al. (2004) reported highly significant bilateral gray matter deficits in the anterior cingulate cortex, the gyrus rectus and the orbitofrontal cortex in elderly depressed patients compared with healthy controls. Salokangas et al. (2002) found structural differences in the brain of patients with psychotic depression compared with patients with non-psychotic depression. They concluded that a larger white matter volume is typical of non-psychotic depression and enlarged cerebral ventricles and sulcal cerebrospinal fluid volumes are prevalent in psychotic depression.

### 2.4.1. SPECT and PET studies in depression

#### 2.4.1.1. CBF imaging studies in depression

In all the following CBF imaging studies there has been one main methodological limitation, namely psychopharmacological medication. Some of these studies had a very short prior drug-free period, such as five days or more (Devous et al. 1993, Thomas et al. 1993), at least ten days (Amsterdam and Mozley 1992), or at least two weeks (Mozley et al. 1996). In some studies certain patients had taken medication and others in the same study had had a drug-free period or had never taken medication (Austin et al. 1992, Bench et al. 1992, Dolan et al. 1992 and 1994, Maes et al. 1993, Ebmeier et al. 1997, Fischler et al. 1996). In some cases the patients had all taken medication during the study (Ring et al. 1994, Mayberg et al. 1994, Ito et al. 1996). All the investigations used HRSD or MADRS and some used neuropsychological tests. The age of the patients has varied from 36 $\pm$ 10 years (Maes et al. 1993) to 64 $\pm$ 10 years (Ring et al. 1994), while sample sizes have varied from 11 (Ito et al. 1996) to 40 (Austin et al. 1992). In most of the studies the controls were age- and gender-matched. The studies are summarised in Table 1.

Using [$^{99m}$Tc]exametazime SPECT, Austin et al. (1992) demonstrated a significantly decreased uptake in temporal, inferior frontal and parietal regions in depressed patients compared with controls. There was also a strong positive association between uptake and scores on the depression scale, especially in cingulate areas and the frontal cortex. In a study utilizing [$^{123}$I]iodo-amphetamine

(IMP) SPECT there was increased IMP activity in the right temporal lobe among both depressed patients and controls, but this asymmetry was more pronounced in the depressed patients (Amsterdam and Mozley 1992). Devous et al. (1993) found that there was significant difference in rCBF ratios measured with $^{133}$Xe SPECT between different depressive subtypes and normal controls. Endogenous and psychotic groups were similar; they differed from the nonendogenous group in similar areas, which were mostly the same as those in which they differed from normal control subjects.

There have been studies indicating that cortical CBF may be relatively intact in depressed patients when examined with [$^{99m}$Tc]HMPAO SPECT (Maes et al. 1993, Mozley et al. 1996). Other investigators have recorded significant decreases in CBF in depressed patients in paralimbic regions, and specifically in the inferior frontal and cingulate cortex (Mayberg et al. 1994) and the superofrontal cortex (Fischler et al. 1996) by using [$^{99m}$Tc]HMPAO SPECT. Using the same radioligand, Ito et al. (1996) also observed significant decreases in CBF in the prefrontal cortices, limbic systems and paralimbic areas in both unipolar and bipolar depression groups compared with a normal control group. Thomas et al. (1993) studied the rCBF of 42 drug-free inpatients suffering from major depression (n = 21) or dysthymia with major depression (n = 21) using [$^{99m}$Tc]HMPAO SPECT. The patients with major depression had a significantly lower frontal and posterior rCBF ratio than patients with double depression. No correlation was found between the severity of illness and rCBF. These results indicate that there may be different qualitative cerebral dysfunctions in these two affective disorder sub-types. In a [$^{99m}$Tc]HMPAO SPECT study by Ebmeier et al. (1997), an increase in depression scores was associated with an increase in the perfusion of the fronto-limbic brain area and posterior cingulate. Furthermore, increased depression with high levels of stress and anxiety was correlated with reduced frontal neocortical perfusion.

Data from PET studies indicate that depressed patients have regional decreases in cerebral perfusion, localized mostly to the frontal and prefrontal cortices, when compared with healthy controls (Bench et al. 1992, Biver et al. 1994). Ring et al. (1994) compared depressed patients with or without Parkinson's disease with normal controls and with patients with Parkinson's disease but without depression. They

found bilateral decreases in rCBF in the medial prefrontal cortex in both depressed patients groups with and without Parkinson's disease. Dolan et al. (1992) reported that there was a decrease in rCBF in the medial prefrontal cortex in depressed patients with cognitive impairment. They found also in another study that neuropsychological deficits in depression are associated with abnormalities in regional brain function and particularly with the function of the medial prefrontal cortex (Dolan et al. 1994).

#### 2.4.1.2. Transmitter specific imaging studies in depression

The prior psychopharmacological medication is the main methodological difference when comparing the transmitter-specific imaging studies of depression. Only two studies have been performed on drug-free patients (Dahlström et al. 2000, Neumeister et al. 2001). Relatively short prior drug-free periods were used in four studies varying from at least seven days (D'haenen and Bossuyt 1994, Brunswick et al. 2003) to at least three weeks (D'haenen et al. 1992, Malison et al. 1998). In other studies the prior drug-free period was longer, from at least six weeks (Meyer et al. 1999) or at least three months (Shah et al. 1997) to at least six months (Willeit et al. 2000). A small sample size was one limitation in some studies (Willeit et al. 2000, Malison et al. 1998, Shah et al. 1997, Neumeister et al. 2001 and Brunswick et al. 2003). The age of the patients has varied from seven years (Dahlström et al. 2000) to 45 years (Shah et al. 1997). The severity of depression has mainly been assessed using the HRSD, and the mean HRSD scores have differed little between the studies. The studies are summarised in Table 2.

D'haenen and Bossuyt (1994) observed higher basal ganglia/cerebellum ratios in depressed patients than in controls, which could indicate an increase in $D_2$ receptor density in depression. Ebert et al. (1996) reported similar findings in patients with psychomotor retardation. These findings suggest that up-regulation of receptor density may be a secondary mechanism that compensates for a decrease in postsynaptic (second messenger) dopamine function. Utilizing [$^{123}$I]IBZM SPECT, Shah et al. (1997) found that IBZM binding to $D_2$ receptors was correlated with the reaction time and verbal fluency in depressed patients. Parsey et al. (2001)

compared 9 depressed patients with 10 matched healthy controls before and after amphetamine administration using [$^{123}$I]IBZM SPECT. They found no significant differences in preamphetamine $D_2$ receptor availability between depressed patients and controls. The amphetamine-induced reduction in tracer uptake was similar in both groups and the investigators suggested that stimulant-induced dopamine release was not altered in major depression.

Brunswick et al. (2003) recently reported that the specific uptake values of [$^{99m}$Tc]TRODAT-1 binding were significantly higher in the right anterior putamen, right posterior putamen, left posterior putamen and left caudate nucleus of depressed patients than in the comparison subjects. They suggested that dopamine transporter affinity may be higher than normal in the basal ganglia of depressed patients. Hietala et al. (1999) found that depressive symptoms in schizophrenic patients were associated with a decrease in dopamine synthesis. The striatal dopamine synthesis capacity was studied with PET using 6-[$^{18}$F]fluorodopa (FDOPA) as a ligand in 10 neuroleptic-naive schizophrenic patients and 13 healthy controls. Left striatal FDOPA uptake values correlated negatively with depressive symptoms.

A study by D'haenen et al. (1992) using [$^{123}$I]ketanserin SPECT showed a higher uptake of the tracer in the parietal cortex of the depressed patients, and greater right than left asymmetry in the infero-frontal region of the depressed patients, which was not recorded in the control subjects. This finding suggests that there may be higher parietal 5-$HT_2$ receptor densities in depression. A [$^{18}$F]setoperone PET study by Meyer et al. (1999) produced a negative finding, and the authors concluded that the 5-$HT_2$ binding potential is not increased in untreated depressed patients who have not made recent suicide attemps. They assumed that this finding might indicate that 5-$HT_2$ receptors have a role in treatment or that 5-$HT_2$ receptors are increased in highly suicidal states. Sargent et al. (2000) studied major depressed patients using selective 5-$HT_{1A}$ receptor antagonist [carbonyl-$^{11}$C]WAY-100635 PET before and during treatment with selective serotonin reuptake inhibitors. The binding potential values were reduced in the frontal, temporal and limbic cortices in both unmedicated and medicated depressed patients compared with healthy controls. There were no significant differences between these two patients groups. Using [$^{11}$C]RTI-32 PET, a significantly lower DAT binding potential has been detected in the striatum of patients

with current major depressive episodes than in healthy controls, which may due to a down-regulation secondary to lower dopamine concentrations (Meyer et al. 2001).

Malison et al. (1998) were the first to show a reduction in the density of brain SERT binding sites in living depressed patients. When studying drug-free depressed patients with seasonal affective disorder, Willeit et al. (2000) found reduced SERT availability and Neumeister et al. (2001) reduced striatal DAT binding sites. Depressive child and adolescent patients have also been reported to have significantly higher SERT availability ($P < 0.02$) in the hypothalamic/midbrain area (Dahlström et al. 2000).

Table 1. Summary of CBF imaging studies on depression

| Method | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|
| [$^{99m}$Tc] exa-metazime SPECT | HRSD 17 (22±6) Newcastle scale (5±3) | 25/40 drug-free 15/40 AD | n 40<br>age 46 ±14<br>F/M 22/18 | n 20<br>age 47±15<br>F/M 11/9 | ↓ uptake in temporal, inferior frontal + parietal regions depressed vs. NC | Austin et al. 1992 |
| [$^{123}$I]IMP SPECT | HRSD 17 >20 SADS | 14/19 drug-free for at least 10 days | n 19<br>age 41±11<br>F/M 8/11 | n 12<br>age 37±16<br>F/M 3/9 | ↑ IMP activity in R temp lobe in 12/19 of MD and 1/12 NC, in MD R>L | Amsterdam & Mozley 1992 |
| $C^{15}O_2$ PET | HRSD 17 (25±4) MADRS (30±6) SADS RDC | 19/33 drugs on<br>6/33 drug-naive<br>2/33 drug-free for at least 1 year<br>5/33 drug-free for at least 2 wks | n 33<br>age 57±13<br>F/M 12/21 | n 23<br>age 63±12<br>F/M 13/10 | ↓ rCBF in L anterior cingulate and L dorsolat prefront cortex in MD vs. NC<br>↑ rCBF in L medial front gyrus +<br>↑ rCBF in cerebellar vermis MD+cognitive impairment vs. MD without cognitive impairment | Bench et al. 1992 |
| $C^{15}O_2$ PET | HRSD 17 (25) MMSE cognitive function assessment SADS RDC | 19/33 on drugs<br>8/10 on drugs in cognitive impairment group<br>4/10 on drugs in cognitive unimpairment group | cognitive impaired<br>n 10<br>age 61±8<br>F/M 6/4<br>cognitive unimpaired<br>n 10<br>age 53±15<br>F/M 2/8 | comparison of depressed patients with and without cognitive impairment | ↓ rCBF in left anterior medial prefront cortex and<br>↑ CBF in cerebellar vermis in depressed patients with cognitive impairment compared with depressed without cognitive impairment | Dolan et al. 1992 |

Table 1. (continued)

| Method | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|
| $C^{15}O_2$ PET | HRSD 17<br>Primary depressed (24±5)<br><br>depression + Parkinson (22±3)<br>Parkinson (5±2) | antiparkinson medication | Primary depressed<br>n 10<br>age 64 ±10<br>F/M 4/6<br>depressed+ Parkinson<br>n 10<br>age 62±13<br>F/M 4/6<br>Parkinson<br>n 10<br>age 64±10<br>F/M 4/6 | n 10<br>age 66±10<br>F/M 4/6 | ↓ rCBF in anteromedial regions of the medial front and cingulate cortex in depressed Parkinson patients vs. NC and Parkinson without depression<br>Both depressed groups similar | Ring et al. 1994 |
| [$^{133}$Xe] SPECT | HRSD 17<br>all patients (25±7)<br>EN (25±7)<br>PS (30±7)<br>NE (19±4)<br>RDC<br>SADS-L | all drug-free for at least 5 days | total n 47<br>endogen EN 23<br>psychotic PS 11<br>nonendog NE 13<br>age 39±13<br>F/M 35/12 | n 138<br>age 37±13<br>F/M 69/69 | EN + PS similar<br>NC vs. NE ↓ rCBF R middle temp<br>NC vs. PS ↓ rCBF L sup front, R middle temp, ↓ L/R gradient sup frontal + infer temp, ↓ A/P gradient L sup front/inf temp<br>NC vs. EN ↓ rCBF L infer temp, ↓ L/R gradient inf temp, ↓ A/P gradient L sup front/inf temp<br>NE vs. PS ↓ rCBF R middle temp, ↓ L/R gradient sup frontal<br>NE vs. EN ↓ rCBF R middle temp and L infer temp, ↓ L/R gradient sup frontal | Devous et al 1993 |
| [$^{99m}$Tc] HMPAO SPECT | MADRS<br>MD (33)<br>Dyst. (27) | all drug-free for at least 5 days | n 21<br>age 40±10<br>F/M 9/12 | dysthymia<br>n 21<br>age 38±10<br>F/M 12/9 | MD: ↓ rCBF front and post cortex | Thomas et al. 1993 |
| [$^{99m}$Tc] HMPAO SPECT | HRSD 17<br>minor depression (18±3)<br><br>MD (22±3)<br><br>melancholia (26±4)<br><br>SCID | 22/43 drug-free for at least 6 wks<br>21/43 drug-free at least 14 days | minor depression<br>n 12<br>age 36±10<br>F/M 9/3<br>major depression<br>n 18<br>age 47±13<br>F/M 13/5<br>melancholia<br>n 13<br>age 58±13<br>F/M 8/5 | n 12<br>age 39±16<br>F/M 6/6 | no significant differences between patients and NC, cortical CBF was relative intact | Maes et al. 1993 |

| Method | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|
| [$^{99m}$Tc] HMPAO SPECT | HRSD (22±5) MMSE (29±1) HAM-A (18±6) apathy scale (24±9) | On drugs | n 13<br>age 42±11<br>F/M 10/3 | n 11<br>age 35±13<br>F/M 2/9 | ↓ CBF in paralimbic, inf frontal and cingulate cortex in MD vs. NC | Mayberg et al. 1994 |
| [$^{99m}$Tc] HMPAO SPECT | HRSD (11±8) MMSE (26±5) | On drugs 11/11 tricyclic AD | unipolar MD<br>n 11<br>age 67±7<br>F/M 7/4<br>bipolar MD<br>n 6<br>age 67±6<br>F/M 1/5 | n 9<br>age-matched<br>age 66±11 | ↓ CBF in prefrontal cortices, limbic systems and paralimbic regions in unipolar and bipolar MD vs. NC | Ito et al. 1996 |
| [$^{99m}$Tc] HMPAO SPECT | HDRS 17 (23±4) SCID | all drug-free for at least 2 wks | n 19<br>age 38±10<br>F/M 6/13 | n 16<br>age 39±11<br>F/M 7/9 | no significant differences between patients and NC | Mozley et al. 1996 |
| [$^{99m}$Tc] HMPAO SPECT | HRSD 17 CAS | drug-free for at least 1 wk 4/19 BZD | n 19<br>age 40±12<br>F/M 15/4<br>CFS<br>n 16<br>age 35±10<br>F/M 14/2 | n 20<br>age 36±9<br>F/M 8/12 | ↓ CBF superofrontal in MD compared with both CFS and NC R>L parietotemporal in CFS vs. MD | Fischler et al. 1996 |
| [$^{99m}$Tc] HMPAO SPECT<br>2 scans within 12 hours | HRSD 17 (26±6) Newcastle score, personality question-naire BFS, APSAQ, SAI, DSST, AVLT | 5/20 drug-naive 15/20 drug-free 2 wks 1/20 ECT within the last 6 months | n 20<br>age 44±12<br>F/M 12/8 | morning and evening scans were compared | depression severity and independent vital depression factor in subjects with ↑ CBF in cingulate and paralimbic areas, ↑ anxious-depress factor + ↓ rCBF front neocortical | Ebmeier et al. 1997 |
| [$^{99m}$Tc]ECD SPECT | HRSD psychotic MD (35±7) non-psychotic MD (27±7) SCID | drug-free at least 1 month | psychotic MD<br>n 9<br>age 41±11<br>F/M 4/5<br>non-psychotic MD<br>n 12<br>age 37±10<br>F/M 9/3 | n 1 2<br>age 34±8<br>F/M 6/6 | ↓ rCBF in the subgenual portion of the left anterior cingulate cortex in psychotic MD compared to NC and non-psychotic MD | Skaf et al. 2002 |

Table 1. (continued)

| Method | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|
| [$^{99m}$Tc] HMPAO SPECT | HRSD<br>HAS<br>Newcastle<br>DMS | drugfree at least 2 wks | n 50<br>age 41±11<br>F/M 35/15<br>atypical<br>n 14<br>melancholic<br>n 16<br>somatic<br>n 32<br>undifferent<br>n 9<br><br>(note: overlapping between depressive symptoms) | n 20<br>age 35±9<br>F/M 14/6 | ↓ CBF in all depressed patients across all subtypes (82% of MD had abnormal SPECT findings)<br>atypical: left occipital lobe hypoperfusion<br>melancholic and undifferentiated: bilateral temporoparietal, right caudate nucleus and left globus pallidus hypoperfusion | Fountoulakis et al. 2004 |
| [$^{99m}$Tc] HMPAO SPECT | HRSD 17-item<br>DwoPF (31±5)<br><br>DwPF (31±7)<br><br>SCID | only BZD | no psychotic (DwoPF)<br>n 16<br>age 42±6<br>F/M 12/4<br><br>with psychotic features (DwPF)<br>n 12<br>age 38±10<br>F/M 9/3 | n 16<br>age 37±9<br>F/M 13/3 | ↓ rCBF in depressed patients in the both sup front cortex and L ant cingulate cortex<br>DwPF : ↓ rCBF in L parietal cortex, L cerebellum but ↑ rCBF in the L inf front cortex and caudate nucleus | Gonul et al. 2004 |

BZD = benzodiazepine medication, MD = major depression, NC = normal controls, L = left, R = right, A = anterior, P = posterior, AD = antidepressant, F = female, M = male, CFS = chronic fatigue syndrome, DwoPF = depressive patients without psychotic features, DwPF = depressive patients with psychotic features

Table 2. Summary of transmitter specific imaging studies on depression.

| Method | | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|---|
| 2-[$^{125}$I] ketanserin SPECT | 5-$HT_2$ | HRSD 17 (23±5) | 9/19 AD drug-free < 3 wks 10/19 AD drug-free > 3 wks | n 19<br>age 45±14<br>F/M 13/6 | n 10<br>age 36±11<br>F/M 5/5 | ↑ 5-$HT_2$ receptor density in parietal cortex of MD vs. NC, ↑ R>L infero-frontal region in MD | D'haenen et al. 1992 |
| [$^{123}$I]IBZM SPECT | $D_2$ | HRSD 17 (22±5) SCID | Drug-free at least 7 days | n 21<br>age 41±12<br>F/M 17/4 | n 11<br>age 41±8<br>F/M 8/3 | ↑ $D_2$ receptor density in MD vs. NC | D'haenen and Bossuyt 1994 |
| [$^{123}$I]IBZM SPECT | $D_{2/3}$ | HRSD 17 (24±8) Newcastle Scale | Drug-free at least 3 months | n 14<br>age 45±14<br>F/M 6/9 | n 15<br>age 41±10<br>F/M 6/9 | ↑ R striatal activity in MD vs. NC, signif. correl. between IBZM-binding in bilat striatum + reaction time and verbal fluency | Shah et al. 1997 |
| [$^{123}$I]β-CIT SPECT | SERT | HRSD 19 SCID HAM-A BDI CGI | Drug-free at least 3 wks | n 15<br>age 44±10<br>F/M 8/7 | n 15<br>age 45±11<br>F/M 8/7 | ↓ SERT availability in brainstem in MD vs. NC | Malison et al. 1998 |
| [$^{18}$F]setope-rone PET | 5-$HT_2$ | HRSD 17 (23±4)<br>SCID | Drug-free at least 6 wks no recent suicide attempts | n 14<br>age 18-40 | n 19<br>age 18-45 | no increased 5-$HT_2$ binding prefrontal cortex | Meyer et al. 1999 |
| [$^{123}$I]β-CIT SPECT | SERT | SCID SPAQ (GSS) SIGH-SAD | Drug-free at least 6 months | n 11<br>age 31±8<br>F/M 9/2 | n 11<br>age 29±6<br>F/M 9/2 | ↓ SERT density in thalamus-hypothalamus in depressed SAD vs. NC | Willeit et al. 2000 |
| [$^{11}$C]WAY-100635 PET | 5-$HT_{1A}$ | HDRS unmedic (22) medic (8)<br>BDI unmedic (23) medic (12) | | unmed UM<br>n 15<br>age 38±14<br>F/M 0/15<br>medic M<br>n 20<br>age 43±15<br>F/M 3/17 | n 18<br>age 36±8<br>F/M 1/17 | ↓ 5-$HT_{1A}$ receptor binding front, temp and limbic cortex in both UM and M MD vs. NC | Sargent et al. 2000 |

Table 2. (continued)

| Method | | Diagnostics (mean) | Medication | Depressed | Controls | Findings | Ref. |
|---|---|---|---|---|---|---|---|
| [$^{123}$I]β-CIT SPECT | SERT (DAT) | C-SSAGA CDI | drug-naive | n 31<br>age 7-17<br>F/M 9/22 | n 10<br>age 8-16<br>F/M 5/5 | ↑ SERT availability in hypothalamus /midbrain in depressed | Dahlström et al. 2000 |
| [$^{123}$I]β-CIT SPECT | DAT | SCID<br>SIGH-SAD >19 | drug-naive | SAD<br>n 11<br>age 31±8<br>F/M 10/1 | n 11<br>age 31±10<br>F/M 10/1 | ↓ DAT binding in L striatum in depressed SAD patients vs. NC | Neumeister et al. 2001 |
| [$^{99m}$Tc]TRO-DAT-1 SPECT | DAT | HRSD 17 (22±4)<br>SCID | Drug-free at least 7 days | n 15<br>age 40±12<br>F/M 6/9 | n 46<br>age 40±11<br>F/M 24/22 | ↑ DAT availability R A putamen, R and L P putamen, L caudatum in MD vs. NC | Brunswick et al. 2003 |

MD = major depression, NC = normal controls, L = left, R = right, A = anterior, P = posterior, AD = antidepressant, F = female, M = male, SAD = seasonal affective disorder

## 2.5. Recovery from depression

The term 'response' generally means that a depressed patient has experienced at least a 50% reduction in symptoms as assessed on a standard psychiatric rating scale. Remission is a term used when essentially all symptoms have disappeared and a patient is asymptomatic. According to the HRSD, a patient is asymptomatic if the score is less than 7. The definition of recovery is that the patient has been asymptomatic for at least 6 months. Respectively, according to the BDI, asymptomatic patients have a score of less than 8 and the definition of recovery is an asymptomatic period of more than 4 months (Frank et al. 1991). Recovery from depression depends on the sample: the outcome varies according to whether the depression is observed in the general population or in clinical populations. According to Netherlands Mental Health Survey and Incidence Study (NEMESIS), a poor outcome of major depression was usual in the general population (Spijker et al. 2001).

Recovery from depression depends on many factors, which differ between the general and clinical populations. The NEMESIS study showed that potential risk

factors for a poor outcome of major depression in the general population were female gender, unemployment, a younger age, the severity of depression, the presence of psychotic symptoms, a longer duration of previous episodes, psychomotor agitation or retardation, the presence of anhedonia, early awakening, comorbidity with dysthymia and with anxiety disorders, high neuroticism and multiple negative life events and one or more ongoing difficulty during the follow-up period (Spijker et al. 2001).

DSM-III introduced clusters in personality disorders (PDs): cluster A PDs, odd (paranoid, schizoid and schizotypal personality disorders); cluster B PDs, dramatic (borderline, histrionic, narcissistic and antisocial personality disorders); and cluster C PDs, anxious (dependent, avoidant and obsessive-compulsive personality disorders) (Gunderson and Phillips 1995). Rossi et al. (2001) reported that the most common personality disorders (PDs) with major depression were avoidant PD (31.6%), borderline PD (30.8%) and obsessive-compulsive PD (30.8%). Viinamäki et al. (2002) demonstrated that patients with cluster C PDs recovered from depression less well than patients suffering from pure major depression in a 6-month follow-up study. The results remained the same on 24-month follow-up (Viinamäki et al. 2003).

### 2.5.1. Imaging of recovery from depression

There are three strategies for investigating biological abnormalities in psychiatric disorder: 1) cross-sectional comparison with normal controls, 2) correlation of the biological variable with a relevant clinical variable within the patients group, and 3) longitudinal comparison of patients before and after treatment and/or recovery.

One of the first longitudinal comparison SPECT studies on depressed patients before and after recovery was carried out by Goodwin et al. (1993) with [$^{99m}$Tc]exametazime. It revealed significant bilateral increases in CBF in basal ganglia and the inferior anterior cingulate cortex, and increases in CBF in the thalamus and posterior cingulate cortex on the right side in the patients group matched for drug treatment (n = 16). An unmatched patient group served as controls (n = 12). The total Hamilton scores were similar, but controls showed more guilt, retardation and diurnal variation in mood than patients. The simplest interpretation of these findings

according to the investigators is that the state changes in depressive illness have a topography largely confined to inferior limbic and subcortical regions. Further, their results suggest the involvement of dopaminergic pathways as a possible final common pathway in the expression of state changes in depressive illness. The investigators also reported a persistent reduction in tracer uptake in the neocortex after successful treatment, and they postulated that this significant decrease might be due to trait differences between the patients and controls.

Ebert et al. (1996) concluded from their findings that striatal dopamine release is decreased in the subgroup of depressed patients with psychomotor retardation, and that improvement in depression and retardation leads to an increase in striatal dopamine turnover. Bonne et al. (1996) found that [$^{99m}$Tc]HMPAO uptake was significantly increased in depressed patients who responded to ECT, but remained unchanged in patients who did not respond to the treatment. This finding implies that the reduced rCBF in depression is a state-related property and is reversible by successful treatment. In their [$^{99m}$Tc]ethyl-cisteinate-dimer (ECD) (perfusion) and [$^{123}$I]iomazenil (benzodiazepine receptor function) SPECT study, Mervaala et al. (2001) found that clinically successful ECT was associated with an increased perfusion in right temporal and bilateral parietal cortices and a highly significant increase in the benzodiazepine receptor uptake in all cortical regions except temporal cortices.

Matthew et al. (1996) found that an improvement in depressive symptoms after light therapy was associated with an increase in rCBF in the frontal and cingulate regions and in the thalamus when studied with [$^{99m}$Tc]HMPAO SPECT. Navarro et al. (2002) reported that a significantly lower CBF in the left frontal region detected during the active depression phase disappeared in remission, and there were no significant differences in [$^{99m}$Tc]HMPAO uptake between depressed patients and controls. Further, they found no significant correlations between baseline clinical characteristics of the patients and their perfusion values in depression and in remission.

Larisch et al. (1997) found in their [$^{123}$I]IBZM SPECT study that there was an increase in dopamine $D_2$ receptor binding in the striatum and anterior cingulate gyrus during serotonin reuptake inhibition in treatment responders, but not in

nonresponders. The increase in $D_2$ receptor binding correlated significantly with clinical recovery from depression as assessed with the Hamilton depression rating scale.

Brody et al. (2001) compared two distinct forms of treatment, paroxetine and interpersonal psychotherapy (IPT), and studied patients with unipolar major depression (n = 24) and healthy controls (n = 16) at baseline and on 12-week follow-up using [$^{18}$F] fluorodeoxyglucose (FDG) PET. At baseline, depressed patients had a higher rate of metabolism in the prefrontal cortex and caudate and the thalamus and a lower metabolism in the temporal lobe than the controls. With treatment, these metabolic changes normalized. Patients in both treatment groups showed decreases in prefrontal cortex and left anterior cingulate gyrus metabolism, and increases in left temporal lobe metabolism. The regional metabolic changes were similar in the two treatment groups.

Martin et al. (2001) compared depressed patients treated with venlafaxine hydrochloride (n = 15) and IPT (n = 13). They studied patients at baseline and after six weeks using [$^{99m}$Tc]HMPAO SPECT and MRI. The venlafaxine group had an increase in blood flow in the right posterior temporal and the IPT group in the limbic right posterior cingulate and both groups in the right basal ganglia. Symptoms in both groups improved significantly as measured by clinical rating scales, but there was no significant difference between groups in the alleviation of symptoms.

Drevets et al. (2002) found in their FDG PET study that successful antidepressant treatment led to recovery. They noted that long-term antidepressant treatment reduced metabolism in the amygdala and ventral anterior cingulate cortex in depressed subjects showing a persistent, positive treatment response.

Kugaya et al. (2003b) compared 10 depressed patients who were treated with paroxetine (20 mg/day) for 6 weeks, and 17 healthy controls who were treated with citalopram (40 mg/day) and bupropion (100 mg/day) or only bupropion (100-200 mg/day) for 16 days. [$^{123}$I]β-CIT SPECT scans were performed at baseline, before drug administration, on day 8 and on day 16. SSRI medication significantly increased the striatal DAT binding and decreased SERT binding in the brainstem in both groups. Later, Kugaya et al. (2004) investigated 23 depressed patients treated with fluoxetine (20 mg/day) for 6 weeks and 10 depressed patients who received

paroxetine (20 mg/day) for 6 weeks. [$^{123}$I]β-CIT SPECT scans were performed three times: at baseline, during treatment and after treatment. A higher pre-treatment diencephalic SERT availability was recorded, which significantly predicted a better treatment response, while a greater occupancy of diencephalic transporters by paroxetine correlated with a better treatment response. The investigators concluded that a higher pre-treatment availability and greater occupancy of SERT in diencephalons may predict a better treatment course in response to SSRIs.

When comparing 16 patients with major depression and 16 healthy control subjects using [$^{99m}$Tc]HMPAO SPECT, Ogura et al. (1998) observed significant reductions in CBF in the left superior frontal, bilateral parietal and right lateral temporal cortex in the depressed state. During remission, significant increases in CBF were found in the left superior frontal, right parietal and right lateral temporal cortex. There were no significant differences in tracer uptake between patients in remission and controls. The investigators postulated their findings to suggest that the regional decreases in tracer uptake observed in the depressed state might be a state-related abnormality. Klimke et al. (1999) reported that successful treatment of depression is associated with an increase in the density and/or affinity of striatal dopamine $D_2$ receptors measured by [$^{123}$I]IBZM SPECT.

## 2.6. Epidemiological background of comorbidity

Psychiatric comorbidity is defined as the presence of two or more specific disorders in an individual, either coincidently or consecutively. Comorbidity of mood disorders is considerable in the general population. In their NEMESIS study, De Graaf et al. (2002) reported that 60.5% of the subjects with a mood disorder also had at least one other comorbid disorder, usually anxiety disorder. Only 40% of the subjects with a mood disorder had a pure mood disorder in the 12-month study. The investigators determined that anxiety-comorbid mood disorder was the most prevalent comorbid condition, and was even more prevalent than pure mood disorder. In the same study, 16.7% of the subjects with a mood disorder had a comorbid substance use disorder.

In a 15-year prospective follow-up study, Goldberg et al. (2001) found that 27% of the study group (initially hospitalized for unipolar major depression) had developed

one or more distinct periods of hypomania and another 19% of study group had at least one episode of full bipolar I mania.

A study by Rossi et al. (2001) demonstrated that 63.2% of unipolar major depressive patients had at least one personality disorder with depression. Cluster C PD has been a common finding in depressed outpatients (Oldham et al. 1995, Fava et al. 1996).

Driessen et al. (2001) reported that there were comorbid disorders in alcohol-dependent subjects with major depression (15%) and with anxiety disorder (23%). They also observed the lifetime prevalence of comorbid depressive and/or anxiety disorders to be 38%. Preisig et al. (2001) reported that 67% of patients with alcoholism had comorbid mood disorder and as many as 83% of patients with combined alcoholism and anxiety had comorbid mood disorder. Depressed patients with comorbid alcoholism are at great risk of chronic impairment, and untreated alcoholism worsens depressive states and increases the likelihood of suicide (Thase et al. 2001).

## 2.7. Neuroimaging in other psychiatric disorders comorbid with depression

### 2.7.1. Anxiety disorders

De Cristofaro et al. (1993) assessed brain perfusion in seven patients with panic disorder and in five age-matched controls measured with [$^{99m}$Tc]HMPAO SPECT. They found significant right-left asymmetry in the inferior frontal cortex of the panic patients as well as a significant increase in CBF in the left occipital cortex and a significant decrease in CBF in the hippocampus bilaterally. This finding suggests that the hippocampus may be an important element in the pathophysiology of panic disorder. Edmonstone et al. (1994) compared CBF in obsessive-compulsive disorder (OCD) patients with depressed patients and with normal controls using SPECT with [$^{99m}$Tc]exametazime. They found reduced tracer uptake into basal ganglia of OCD patients compared with drug treated patients and drug-free controls, and observed that reductions in both caudate nuclei and in left putamen correlated with anxiety symptoms.

Using [$^{123}$I]β-CIT SPECT, Tiihonen et al (1997b) reported a decrease in striatal dopamine reuptake sites in patients with social anxiety disorder compared with normal volunteers. This suggests a deficit of dopaminergic innervation in the striatum. The authors gave two explanations for the low dopamine transporter density: first, the number of dopaminergic synapsis and neurons may be reduced, and second, there may be fewer dopamine reuptake sites per neuron. Schneier et al. (2000) found that the mean $D_2$ receptor binding potential in the striatum was significantly lower in patients with social phobia than in the comparison subjects measured with [$^{123}$I]IBZM SPECT. This implicated dopaminergic hypofunction in the striatum in patients with social phobia disorder.

### 2.7.2. Bipolar disorders

There have been very few functional imaging studies of manic patients. The primary reasons may be the difficulties in cooperation required for scans and the fact that acutely manic patients need pharmacotherapy, which makes medication-free studies impractical. Studies that have been conducted to date have mainly concerned bipolar depression patients.

Rush et al. (1982) found that whole brain CBF was elevated in bipolar manic or mixed patients compared to controls when studied with [$^{133}$Xe] SPECT. In a [$^{11}$C]3-N-methylspiperone PET study, Wong et al. (1985) observed no statistically significant difference in the caudate/cerebellar activity ratio between bipolar patients and normal controls. Ito et al. (1996) reported significant decreases in CBF in the prefrontal cortices, limbic systems and paralimbic areas in patients with bipolar depression compared with the normal controls using [$^{99m}$Tc]HMPAO SPECT. Ebert et al. (1993) used [$^{99m}$Tc]HMPAO SPECT to study six in-patients with bipolar depression, six depressed in-patients with residual schizophrenia and eight healthy controls. They found that both patient groups were hypofrontal compared to controls. In the right inferior parietal lobe, the somatosensory stimulation response showed a relative decrease in activity in schizophrenia and a relative increase in activity in affective psychoses. O'Connell et al. (1995) studied 11 bipolar manic patients, 21 acute schizophrenics and 15 healthy controls with [$^{123}$I]IMP SPECT. They observed that

both manic and schizophrenic patients had increased temporal rCBF compared to controls, but more prominently the manic patients.

Tolmunen et al. (2004) presented a female patient with mixed mania (bipolar type II mood disorder) compared with six depressed patients and with ten healthy controls. They studied the patients and healthy controls using [$^{123}$I]nor-β-CIT SPECT, examining the manic patient at baseline and after eight months of psychotherapy, and the depressed patients at baseline and after 12 months of psychotherapy. The healthy controls were only scanned at baseline. The investigators found that the manic patient had an elevated DAT density in the striatum and elevated SERT density in the midbrain at baseline, and that these densities decreased during psychotherapy, while the findings for the depressed patients were opposite.

### 2.7.3. Personality disorders

Brain imaging studies on personality disorders have mainly been performed on patients with antisocial, schizotypal and borderline personality disorders.

An interesting case study revealed an increase in rCBF in the left temporal lobe in a patient with multiple personality disorder (MPD) measured by [$^{99m}$Tc]HMPAO SPECT (Saxe et al. 1992). In another case study, there was hypoperfusion in the right parietal cortex in a depressed patient with mixed-type personality disorder and panic disorder symptoms during hysterical paresthesia (Tiihonen et al. 1995). After recovery from left-side paresthesia, the right parietal lobe perfusion improved by 15.5%. Laakso et al. (2003) found that anxiety-related personality scales, somatic anxiety and muscular tension, and irritability were significantly associated with low [$^{18}$F]fluorodopa uptake in the caudate. According to the investigators, the results suggest a role for the dopaminergic system in the regulation of anxiety in healthy subjects.

Utilizing [$^{99m}$Tc]HMPAO SPECT, Intrator et al. (1997) studied the response of psychopaths to negative affective verbal stimuli by comparing regional cereral blood flow (rCBF) in psychopath and nonpsychopath substance abusers and normal control subjects. They found that psychopaths had a greater increase in rCBF when the words had a negative affective content, whereas the other groups showed greater

activation in the neutral condition. The regions of interest in which the psychopathic group increased their rCBF significantly were the right and left frontal temporal regions and right and left subcortical regions involving the basal ganglia. The investigators concluded that this increase in rCBF may indicate that psychopaths require additional resources to do the emotional task, since emotion is the primary deficit in psychopathy. Although this study was preliminary, it provided support for the hypothesis that there are abnormalities in the way psychopaths process semantic and affective information.

Tiihonen et al. (1997c) observed that the 5-HT specific binding of [$^{123}$I]β-CIT in the midbrain of antisocial violent offenders was lower than that in the healthy controls or in non-violent alcoholics. They suggested that habitual impulsive aggressive behaviour is associated with a decrease in 5-HT transporter density. Significant negative correlations were found between interpersonal features of psychopathology and the frontal and temporal perfusion, and this may indicate that aberrant frontotemporal activity may be a factor in violent behaviour (Söderstrom et al. 2002).

In their pilot SPECT study with patients with schizotypal personality disorder (SPD), Buchsbaum et al. (1997) found that SPD patients showed greater activation in different frontal regions in performance on the Wisconsin Card Sort Test (WCST) than control subjects, possibly as a compensation for dysfunction in other regions. De la Fuente et al. (1994) reported no significant differences in temporal glucose metabolism between patients with borderline personality disorder and control subjects measured with [$^{18}$F]DG PET.

### 2.7.4. Alcoholism and substance abuse

Alcoholic patients with antisocial personality disorder (ASP) exhibited more marked frontal hypoperfusion, and chronic alcoholics with ASP may be more vulnerable to the toxic effect of alcohol. Investigators postulated that the primary disturbance is ASP and the frontal hypoperfusion is the result of a chronic alcohol intake. (Kuruoğlu et al. 1996)

The benzodiazepine receptor distribution volume is significantly lower in the frontal, anterior cingulate and cerebellar cortices in alcoholic subjects than in healthy

controls measured with SPECT and [$^{123}$I]iomazenil (Abi-Dargham et al. 1998). Laine et al. (1999a) reported in their [$^{123}$I]β-CIT SPECT study that striatal DAT binding in alcoholics on admission for detoxification was markedly lower than in the non-alcoholic controls. DAT binding returned to the levels of the healthy controls after a 4-week abstinence. The most substantial recovery occurred after four days of abstinence. In the study of Repo et al. (1999), striatal presynaptic DAT densities were also shown to be significantly lower among type I alcoholics than in controls. Laine et al. (1999b) found a statistically significant correlation between the change in DAT availability and depressive symptom scores during alcohol withdrawal, which might indicate a possible dopaminergic etiology for depressive symptoms in alcohol withdrawal.

In a postmortem study Little et al. (1999), cocaine users had a high number of DAT binding sites in the striatum, but a low number of total dopamine terminals. Jacobsen et al. (2000) observed significant increases in diencephalic and brainstem SERT binding in cocaine-dependent subjects during acute abstinence compared with healthy controls. This finding provided evidence of serotonergic dysfunction during acute abstinence from chronic cocaine use.

## 2.8. Summary based on the literature

These functional imaging studies on depression provide convincing evidence to support the monoamine hypothesis of depression. Dopamine, serotonin and noradrenaline have a notable influence on the pathophysiology of depression. During the past decade, neurotrophins, neural adaptation and plasticity have aroused wider interest and have come under research. There is an unquestionable overlap between the theory of neurotransmission and the theory of neurotrophins in the pathogenesis of depression.

Several perfusion studies have shown in most cases that there is reduced rCBF, particularly in the prefrontal cortex, in depressed patients compared with healthy controls. Continuous development of specific radiolabeling tracers has provided the possibility to examine the binding and availability of receptors and transporters *in vivo* in the human brain by PET and SPECT. Some studies have recorded a higher

density of $D_2$ receptors in depressed patients with psychomotor retardation. These findings suggest that up-regulation of receptor density may be a secondary mechanism that compensates for a decrease in postsynaptic (second messenger) dopamine function. According to a recent investigation, DAT binding may be higher than normal in the basal ganglia of depressed patients (Brunswick et al. 2003). Some studies have suggested that SERT densities are lower in the midbrain regions of depressed patients.

Many of these functional studies have been cross-sectional, which means that depressed patients are compared with healthy controls. When using longitudinal comparison studies we can better observe whether changes in the brain in depression are state or trait dependent. Recovery from depression seems to be associated with an improvement in CBF and the density of striatal $D_2$ receptors, suggesting that impairment of the brain in depression might be a state-related abnormality.

Because these functional studies have had several limitations and methodological differences, and the results have even been contradictory, further research is still needed. It is not known how GABA-benzodiazepine receptors associate with depression. Neither is it not known whether there is a difference in striatal DAT density between depressed patients and healthy controls, or whether cluster C personality disorder affects DAT density in depressed patients. Furthermore, it is not known how recovery from depression affects DAT and SERT densities.

# 3 AIMS OF THE STUDY

To test the hypothesis that the brain benzodiazepine receptor density in drug-naive depressed patients is lower than in healthy controls. (I)

To test the hypothesis that the brain DAT densities in drug-naive depressed patients are lower than in healthy controls. (II)

To determine whether cluster C personality disorder has independent effect on striatal DAT densities in major depression. (III)

To examine how recovery from depression associated with brain DAT and SERT densities. (IV)

# 4 METHODS

## 4.1. Diagnostics and study subjects

The study protocol was approved by the Ethical Research Committee of Kuopio University Hospital. All patients provided written informed consent before entering the study. All patients were evaluated at the Department of Psychiatry, Kuopio University Hospital.

The psychiatric diagnoses were made according to DSM-III-R, which is described in section 2.1.1. (American Psychiatric Association 1987). Diagnoses were verified using the Structured Clinical Interview for DSM-III-R (SCID-I) at baseline (Spitzer et al. 1992). The diagnoses of personality disorders were assessed using the SCID-II-interview, which was conducted six months after the major depression diagnosis in order to exclude any potential incorrect diagnoses made when evaluating during the depressive phase (Zimmermann 1994). The severity of depression in the patients was assessed with the 17-item HRSD (Hamilton 1960), BDI-21 (Beck et al. 1961) and MADRS (Montgomery and Åsberg 1979).

It is well known that personality disorder diagnoses are less reliable than most Axis I diagnoses and they may be state dependent in a large proportion of acutely depressed patients (Stuart et al. 1992). In our studies, SCID-I and SCID-II were administered by an experienced interviewer who had undergone a 3-day training course prior to the study and achieved a total kappa of 0.78 against a trainer experienced in SCID-I and –II diagnoses. A kappa of 0.7-0.8 indicates good reliability (Blacker and Endicott 2000).

Other psychiatric and psychosomatic symptoms were assessed using the 90-item Symptoms Checklist (SCL-90, range in scores 1-5) (Derogatis et al. 1973). Alexithymia was assessed using the 20-item Finnish version of the Toronto Alexithymia Scale (TAS-20) (Joukamaa et al. 2001), whose total scores ranged from 20 to 100 (Bagby et al. 1994, Taylor et al. 1997). The level of the patients' psychosocial functioning was evaluated using the Global Assessment of Functioning Scale (GAF) (range 1-100) (Spitzer et al. 1996).

### 4.1.1. Benzodiazepine receptor density in major depression (I)

Our sample consisted of thirteen treatment-seeking outpatients with major depression and seven healthy controls. The patients were assessed at the beginning of psychiatric care and comprised 7 men and 6 women with a mean age of 44.1 years (SD = 10.6). According to the anamnestic data, none of them had ever received any psychopharmacological treatment. The controls consisted of 3 men and 4 women with a mean age of 39.9 years (SD = 4.4). No statistically significant differences in age or gender were detected between patients and controls. The controls were chosen from among the hospital staff and none had any psychiatric or neurological disorders. The mean Hamilton score among patients was 21.2 (SD = 7.5), and the mean psychic anxiety score, which is item 10 in the HDRS (range 0-4), was 1.6 (SD = 0.9).

### 4.1.2. Striatal dopamine transporter density in major depression (II)

The study subjects consisted of fifteen treatment-seeking outpatients with major depression and eighteen healthy controls. All patients were experiencing a current episode of major depression, with no other accompanying psychiatric diagnoses. The patients had received no antidepressant medication prior to SPECT imaging. The depressed patients comprised five men (33%) and ten women, with a mean age of 36.1 years (SD = 8.1). The control group consisted of eight men (44%) and ten women and had a mean age of 35.2 years (SD = 5.9). No statistically significant differences in age ($p = 0.72$) or gender ($p = 0.52$) were detected between patients and the control group. The controls were chosen from among the hospital staff, none of whom were known to have any psychiatric or neurological disorders, medication or substance abuse. The mean Hamilton score of the patients was 16.3 (SD = 7.4), the mean BDI score 20.1 (SD = 7.3) and the mean MADRS score was 21.0 (SD = 5.8). The results on separate scales indicated that our patients suffered from a moderate level of depression. The psychosocial functional capacity at the time of evaluation was assessed using the Global Assessment Scale (GAS) (Endicott et al. 1976), yielding a mean GAS score of 57.6 (SD = 7.6).

### 4.1.3. Effect of cluster C personality disorder on striatal dopamine transporter densities in major depression (III)

The study subjects comprised 20 outpatients with major depression. The study group was divided into two sub-groups: one with major depression and only cluster C PD (n = 10) and the comparison group with pure major depression and without comorbid personality disorder (n = 10). The clinical characteristics of the groups of patients are presented in Table 3. Fifteen patients were drug-naive, two had occasionally received benzodiazepine medication and three had received antidepressive medication, but there had been a pause of at least one year in medication prior to SPECT imaging. None of the patients had any neurological disorders or histories of alcohol or substance abuse. The control group consisted of eight men (44%) and ten women and had a mean age of 35.2 years (SD = 5.9). The controls were chosen from among the hospital staff, none of whom were known to have any psychiatric or neurological disorders, medication or substance abuse. According to previous findings (Volkow et al. 1996, Kuikka et al.1999), dopamine transporters decrease in density with age (about -0.5% per year) and age-correction was therefore carried out.

### 4.1.4. [$^{123}$I]β-CIT binding and recovery from depression: A six-month follow-up study (IV)

The study group consisted of 18 outpatients with depression. The inclusion criterion was a current diagnosis of depression according to ICD-10 assessed by the attending psychiatrist. The mean HRSD score was 13.9 (SD 6.7) at baseline and 9.8 (SD 6.1) at six-month follow-up, and Cronbach's $\alpha$ for HRSD was 0.76 and 0.78, respectively. Diagnoses were major depression (72%) and other depression (28%) such as dysthymia and reactive depression.

None of the patients were taking psychopharmaceutical medication before the first assessment. During the follow-up period, after the first SPECT scan, six patients used benzodiazepines, one patient moclobemide and temazepam, one amitriptyline and diazepam and one venlafaxin. Before the second SPECT scan, all patients had been drug-free for at least one month. As the depression of the patients was

relatively mild, they were treated primarily with supportive therapeutic interactions and counseling.

After six months of follow-up the median HRSD was 12.0. We then divided the patients according to their HRSD score on follow-up into two groups: the responders (HRSD -score below 12 points) and the non-responders (HRSD -score 12 or more). The mean HRSD score on follow-up was 3.9 (SD 3.1) among responders and 14.6 (SD 2.7) among non-responders. The mean age of responders was 36.4 (SD 11.8) and that of non-responders 47.7 (SD 4.5). The group of responders consisted of one man and 7 women, while the non-responding group comprised 4 men and 6 women. When recovery was defined according to the criteria presented by Frank et al. (1991), 7 subjects had an HRSD score of 7 points or less (responders), and 11 scored more than 7 points (non-responders).

## 4.2. Image analysis and processing

### 4.2.1. [$^{123}$I]iomazenil (I)

A dose of 160-210 MBq of [$^{123}$I]iomazenil was used. The SPECT scan was performed 90 minutes after injection of the tracer using a three-head Siemens MultiSPECT 3 gamma camera equipped with fan beam collimators (Siemens Medical Systems Inc., Hoffman Estates, Ill., USA). A total of 4-5 million counts were acquired for the entire head using an angular step of 3° over 360°. Nine-millimeter thick transaxial (oriented in the orbitomeatal line), sagittal and coronal slices were reconstructed using a Butterworth filter (order of 8.0 and cut-off frequency of 0.75 $cm^{-1}$). The Chang attenuation correction was applied with the uniform attenuation coefficient of 0.10 $cm^{-1}$. The imaging resolution was set at 8-9 mm. A semi-automatic brain quantification program, which was included in the Siemens MultiSPECT 3 gamma camera, was used to analyze the regions of interest (ROI). Regional count densities (rCBF) were calculated. Regional counts were related to the average cerebellar counts, and the average cortical counts were recorded.

All imaging data were digitized and analyzed by a physicist who was well acquainted with the semi-automatic quantification program and was totally blind to all

data concerning the study subjects, such as the clinical background of the patients and the classification of the patients and controls. With the semi-automatic program she made a drawing of the ROIs in one side of the brain and the program reflected the other side of the brain regions semi-automatically. The program also counted the pulses and straightened the transversal, coronar and sagittal slices. The statistical analyses were performed on the rater's digitized numerical values, which were related to the average cerebellar counts. The average cortical counts were also recorded.

### 4.2.2. [$^{123}$I]β-CIT (II, III and IV)

A dose of 110-185 MBq of [$^{123}$I]β-CIT (supplied by MAP Medical Technologies Inc., Tikkakoski, Finland) was administered intravenously in a dimly lit and quiet room. The affinity, radiolabeling, radiochemical purity, radiopharmaceutical safety and the dosimetry of [$^{123}$I]β-CIT have been previously presented (Neumeyer et al. 1991, Kuikka et al. 1993 and 1994, Bergström et al. 1994). The specific activity was greater than 1.1 x $10^{14}$ Bq/mmol. The average radiation load received by the subjects was 4 mSv, as given by the effective dose equivalent (Kuikka et al. 1994). The SPECT scan was performed 21-24 hours after injection of the tracer using a three-head Siemens MultiSPECT 3 gamma camera equipped with fan beam collimators (Siemens Medical Systems Inc., Hoffman Estates, Ill., USA). In the follow-up study (IV) the SPECT scan was performed 1h and 21-24h after injection of the tracer at baseline and after six months of follow-up. The subject's head holder was specifically built for the Siemens MultiSPECT 3. A full 360 ° rotation was performed (40 views per camera head, each 40 s) at an imaging resolution of 8-9 mm.

Transaxial slices, 3 mm thick and oriented in the orbitomeatal line (OM line) were reconstructed using a Butterworth filter (order of 8.0 and cut-off frequency of 0.75 $cm^{-1}$). The Chang attenuation correction was applied with the uniform attenuation coefficient of 0.10 $cm^{-1}$. Three consecutive slices were summed in order to obtain a total slice thickness of 9 mm and visually surveyed. A semi-automatic brain quantification program from Siemens was used to analyze the regions of interest (ROI). The regions of interest were drawn on both the white matter (as a free

and non-specific binding) and the striatum. The technician who performed the ROI analysis did not know the histories of the subjects and did not perform the scanning. The regional counts were corrected by the radioactivity decay of $^{123}I$, and the average count densities were used for calculations. The striatum-to-white matter ratio was calculated for the right and left sides. The specific binding in the midbrain was calculated from 1-hour data (IV) as (midbrain-cerebellum)/cerebellum.

## 4.3. Statistical analysis

Statistical analysis was performed using SPSS for Windows, release 8.0 (SPSS Inc., Chicago, Ill.). The means, standard deviations (SD), frequencies and percentages were used for description of the continuous variables. We tested our hypothesis by using t-tests for independent samples and Levene's test for equality of variances, and the non-parametric Mann-Whitney U-test with two-tailed p-values. The normalities of the variables were tested first with the One-Sample Kolmogorov-Smirnov Test. For correlation analysis we used Pearson's correlation coefficients for continuous and normally distributed variables, and Spearman's correlation coefficients for non-parametric and non-normally distributed variables with their respective two-tailed tests. The correlation between the change in [$^{123}I$]β-CIT specific binding in the midbrain and the decrease in the HRSD total score was calculated by using a quadratic polynomial fit in the follow-up study (IV). Two-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare the means of a dependent variable by two grouping variables. Analysis of variance and the analysis of covariance were used to compare the means of the dependent variables between the two patient groups in the cluster C study (III). In all studies the level of statistical significance was defined as $p<0.05$.

In the cluster C study (III) we calculated the effect size (ES) for the difference of means in the patient groups. Cohen (1988) has specified the effect size to mean the degree to which the phenomenon is present in the population. The formula for calculating the ES is: $ES = (m1 - m2) / \sigma$ , where m1 = average of the variable in the first group, m2 = average of the variable in the second group, and $\sigma$ = the pooled standard deviation of the groups.

# 5 RESULTS

## 5.1. Benzodiazepine receptor density in major depression (I)

We found statistically significant differences in [$^{123}$I] uptake between the patients and the controls. Compared to the controls, the patients had a significantly lower benzodiazepine receptor density in the left temporal cortex, as well as lower receptor densities in the right temporal and prefrontal cortices. The highest correlations between anxiety and the benzodiazepine receptor densities were observed in the right ($r = -0.74$, $p < 0.01$) and in the left ($r = -0.73$, $p < 0.01$) temporal cortex (upper level).

## 5.2. Striatal dopamine transporter density in major depression (II)

We found a higher striatal DAT density in depressed patients than in healthy controls (Figure 2). The mean striatum-to-white matter ratio on the right side was 7.3 (SD = 1.3) for the patients and 5.9 (SD = 1.2) for the controls. On the left side, the mean striatum-to-white matter ratio was 7.2 (SD = 1.2) for the patients and 5.9 (SD = 1.1) for the controls. The relative counts for both sides of the basal ganglia region differed between the patients and the controls (Mann-Whitney U-test, $p = 0.002$ on the right side and $p = 0.003$ on the left side). When adjusted for age (ANCOVA: $p = 0.001$ on the right side and $p < 0.001$ on left side) and gender (ANCOVA: $p = 0.004$ on the right side and $p = 0.003$ on the left side), first separately and then simultaneously (ANCOVA: $p = 0.001$ on the right side and $p = 0.001$ on the left side), the differences in DAT density for the basal ganglia regions on both sides remained statistically significant between the patients and the controls. No statistically significant correlations were detected between the severity of depression (MADRS, HRSD and BDI -scores) and DAT density. No statistically significant correlation was detected between the psychomotor retardation score (mean 0.2, SD = 0.56), item number 8 in the HRSD (range 0-4), and DAT density.

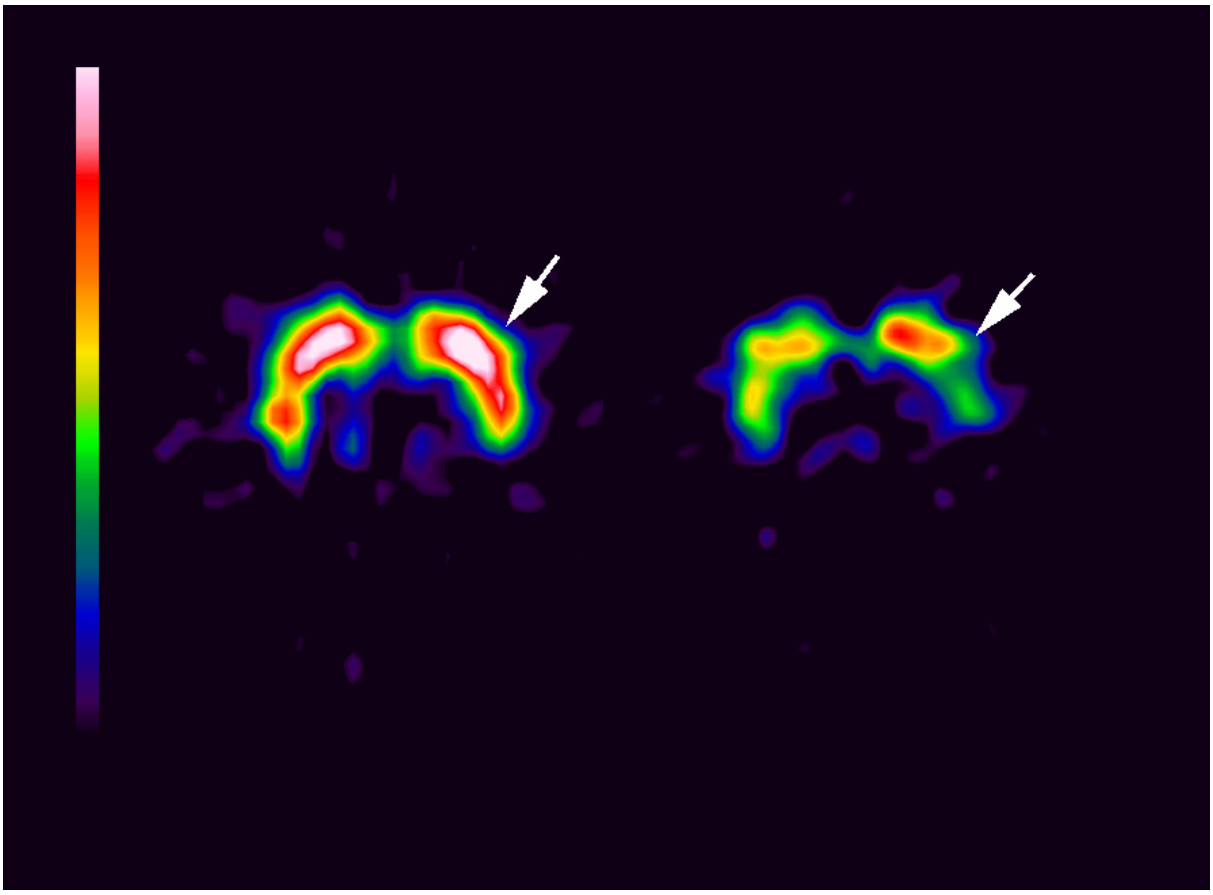

Figure 2. SPECT scans of a depressed patient (left) and a healthy control (right). Arrows indicate the left basal ganglia region. The striatal DAT density is significantly higher in the patient than the healthy control. The increase in DAT density is shown by the brighter colour (white).

## 5.3. Effect of cluster C personality disorder on striatal dopamine transporter densities in major depression (III)

There were no differences in background or in clinical characteristics between the study groups (Table 3). Furthermore, we found no differences in radioligand presynaptic uptake (transporter density) between depression groups, but a difference of over 20% in DAT densities between the depression groups and the control group. There was no significant difference (effect size: 0.28 on the right and 0.17 on the left) in DAT densities between the major depression patients with cluster C PD and those with pure major depression. When DAT densities were compared between patients with major depression and healthy controls, the effect size was 1.44 on both sides of

basal ganglia. Since the confidence intervals of the pure depression group remained within the limits of the confidence intervals of the cluster C PD group, there were clearly no differences in DAT densities among patients with major depression between the groups with or without cluster C PD.

Earlier administration of psychopharmacological medication to some of the patients had no effect on the results. In the analysis of variance (dependent variable: right and left basal ganglia separately; factor: cluster C PD) and when adjusted for age (covariate: age), only age had an effect on DAT density in both sides of basal ganglia region ($p = 0.04$ on the right side and $p = 0.015$ on the left side). Spearman's correlations were calculated between the severity of depression (HRSD score, BDI score) and DAT density in the basal ganglia of the cluster C group (correlation co-efficient for HRSD vs DAT, -0.29 on the right side and -0.27 on the left side; and BDI score vs DAT, 0.26 on the right side and 0.24 on the left side, respectively) and pure depression group (0.19 on the right side and 0.01 on the left side; and -0.27 on the right side and -0.16 on the left side, respectively).

Table 3. Differences in clinical characteristics between the groups.

| Variable | Major depression with cluster C personality disorder (n = 10) | Major depression without cluster C personality disorder (n = 10) | p-value |
|---|---|---|---|
| Age, years (mean ± SD) | 45.0 ± 8.63 | 37.2 ± 11.2 | NS |
| Men, % | 40 | 20 | NS |
| Married or cohabiting, % | 80 | 70 | NS |
| Education<br>Secondary school-leaving examination, % | 30 | 30 | NS |
| Time since first depressive symptoms, patients estimate, years (mean ± SD) | 5.9 ± 7.4 | 4.9 ± 5.2 | NS |
| Current smoker, % | 20 | 20 | NS |
| HRSD score (mean ± SD) | 20.8 ± 4.1 | 17.4 ± 7.4 | NS |
| BDI score (mean ± SD) | 25.6 ± 7.6 | 21.7 ± 4.9 | NS |
| GAS score (mean ± SD) | 52.4 ± 6.4 | 57.8 ± 8.3 | NS |
| TAS score (mean ± SD) | 58.0 ± 12.0 | 56.2 ± 9.9 | NS |
| SCL 90, total score (mean ± SD) | 2.9 ± 0.5 | 2.4 ± 0.3 | NS |
| SCL: anxiety (mean ± SD) | 2.8 ± 0.6 | 2.2 ± 0.5 | NS |
| SCL: OCD (mean ± SD) | 3.3 ± 0.8 | 2.9 ± 0.4 | NS |
| SCL: somatization (mean ± SD) | 2.6 ± 0.7 | 2.5 ± 0.8 | NS |
| SCL: hostility (mean ± SD) | 2.7 ± 1.0 | 2.2 ± 0.5 | NS |

## 5.4. [$^{123}$I]β-CIT binding and recovery from depression: A six-month follow-up study (IV)

The mean relative counts in the midbrain region of the depressed patients were 1.29 (SD 0.13) at the beginning of the study and 1.31 (SD 0.12) on six-month follow-up. The mean relative counts of different brain regions at baseline and on six-month

follow-up among responders and non-responders are presented in Table 4. The decrease in the HRSD scores (0 - 6 months) explained 40% of the change in [$^{123}$I]β-CIT binding in the midbrain.

Table 4. The mean relative counts of different brain regions at baseline and on six-month follow-up among responders and non-responders.

(a) responders

| ROI | baseline (SD) | after 6 months (SD) |
|---|---|---|
| Basal ganglia right | 1.66 (0.29) | 1.76 (0.18) |
| Basal ganglia left | 1.69 (0.31) | 1.75 (0.19) |
| Cingulus | 1.12 (0.10) | 1.12 (0.13) |
| Midbrain | 1.25 (0.14) | 1.35 (0.10) |
| Thalamus right | 1.59 (0.11) | 1.56 (0.11) |
| Thalamus left | 1.58 (0.13) | 1.59 (0.09) |
| Basal ganglia right 24h | 7.53 (0.50) | 7.82 (1.27) |
| Basal ganglia left 24h | 7.84 (0.47) | 7.88 (1.26) |

(b) non-responders

| ROI | baseline (SD) | after 6 months (SD) |
|---|---|---|
| Basal ganglia right | 1.72 (0.19) | 1.62 (0.08) |
| Basal ganglia left | 1.77 (0.18) | 1.63 (0.10) |
| Cingulus | 1.10 (0.10) | 1.10 (0.10) |
| Midbrain | 1.32 (0.12) | 1.28 (0.13) |
| Thalamus right | 1.63 (0.14) | 1.49 (0.10) |
| Thalamus left | 1.59 (0.19) | 1.57 (0.16) |
| Basal ganglia right 24h | 6.92 (1.15) | 7.91 (1.19) |
| Basal ganglia left 24h | 6.94 (1.33) | 7.91 (1.45) |

ROI = regions of interest

Basal ganglia 24h = basal ganglia 24 hours after injection

When assessing the increase in [$^{123}$I]β-CIT binding for the midbrain region, age and gender were used as covariates. The difference between the responders (n = 8) and the non-responders (n = 10) was statistically significant (ANCOVA: F = 8.12; df = 1, 14; p = 0.013). When the recovery criteria of Frank et al. (1991) were used (responders = 7 or less points and non-responders = more than 7 points), the difference in the increase in [$^{123}$I]β-CIT binding (= change) between responders (n = 7; change = + 0.09) and non-responders (n = 11; change = - 0.02) remained significant (ANCOVA: F = 6.91; df = 1, 14; p = 0.020). The patients who recovered from depression had an increase in [$^{123}$I]β-CIT binding in the midbrain (Figure 3). The

difference between the responders and the non-responders in [$^{123}$I]β-CIT binding in the midbrain region at the six-month follow-up was also statistically significant (ANCOVA: F = 6.98; df = 1, 14; p = 0.019). There were no significant differences in [$^{123}$I]β-CIT binding between the responders and the non-responders in other brain regions.

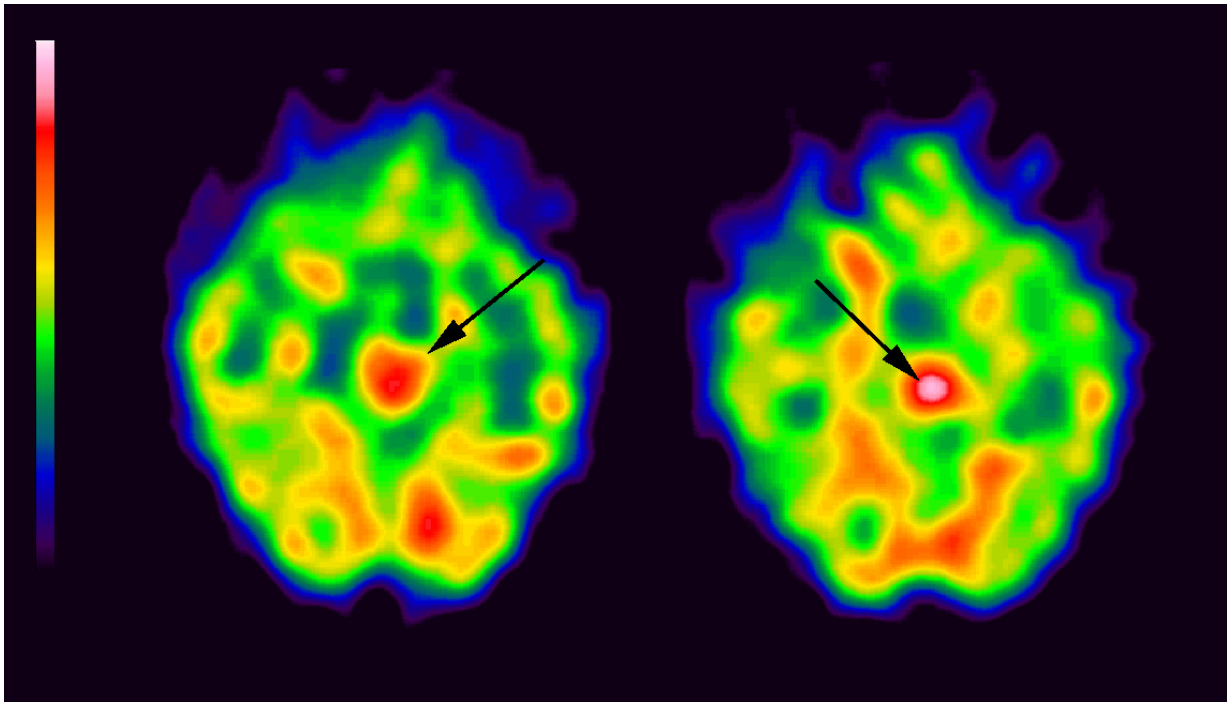

Figure 3. SPECT scan of a recovered patient before (left) and after recovery (right) from depression. The arrows indicate the midbrain region. The increase in [$^{123}$I]β-CIT binding is shown as brighter colour (white).

# 6 DISCUSSION

## 6.1. Benzodiazepine receptor density in major depression (I)

### 6.1.1. Lower benzodiazepine receptor densities in several brain regions

Our results showed that the densities of benzodiazepine receptors within several areas of the brain were lower in depressed patients than in the controls. The decrease in the benzodiazepine receptor density was most prominent in the left temporal lobe. Our results are in accordance with earlier studies implicating GABA-benzodiazepine receptor density in the pathogenesis of anxiety (Sadzot and Frost 1990).

We also found a significant decrease in the regional uptake of the temporal cortex, which is partly in line with the results obtained from previous studies on panic disorder patients (Feistel 1993, Kaschka et al. 1995), and on patients with GAD (Tiihonen et al. 1997a). We suggest that the benzodiazepine receptor density in the left temporal pole of depressed patients resembles that of patients with GAD or panic disorder. Our patients also had lower densities of benzodiazepine receptor in the right temporal pole, prefrontal cortices and both hemispheres. However, it might be possible that our results did not separate the effects of tracer delivery from the binding, due to the relatively short interval (90-120 min) used between injection and scanning. Therefore, these results are offered as semiquantitative target-to-cerebellum ratios, and not as ”true” specific bindings.

### 6.1.2. Anxiety and altered GABA-benzodiazepine function

Anxiety may also be caused by altered GABA-benzodiazepine function resulting from increased endogenous inverse agonism, benzodiazepine receptor spectrum changes, decreased endogenous agonism or a combination of these (Busatto et al. 1997). The same mechanism may be possible in major depression. Furthermore, since receptor spectrum changes per se would not change the number of receptors,

it can be assumed that the lower number of receptors (which correlated with anxiety) is associated with decreased agonism.

### 6.1.3. Comparison of studies on benzodiazepine receptor densities in major depression

We found statistically significant differences between major depression patients and controls in benzodiazepine receptor density. To date, there has been only one other study about benzodiazepine receptor density in major depression, and to our knowledge, our study was the first to describe such a difference. The other study, performed by Kugaya et al. (2003a), failed to detect altered benzodiazepine binding in depressed patients compared with healthy controls using [$^{123}$I]iomazenil SPECT. Prior psychopharmacological medication was one difference between these two studies. Our patients were drug-naive, since they never had been administered psychopharmacological medication. Ten out of thirteen patients of the study by Kugaya et al. had received prior medication, although they had at least a one-month wash-out period before the SPECT scan. This may be one reason behind the difference in results. Patients in Kugaya's study were younger, the mean age being 39.7 $\pm$ 9.8 (9 men, 4 women), and their mean HRSD was 24.6 $\pm$ 3.5, but these differences are unlikely to explain different results of these two studies.

#### 6.1.3.1. Strengths and limitations

The strength of our study was that our patients were drug-naive.The limitations of our study and the study by Kugaya et al. (2003a) were a small sample size, which decreases statistical power, and that iomazenil binds relatively nonselectively to several subtypes of $GABA_A$ receptors. The development of $GABA_A$ subtype selective ligands is needed in the future to investigate benzodiazepine receptors.

## 6.2. Striatal DAT density in major depression (II)

### 6.2.1. Psychomotor retardation and DAT density in major depression

We found no correlation between psychomotor retardation and DAT density, as did Ebert et al. (1996), but it must be noted that our depressed patients did not suffer from severe psychomotor retardation. It is not possible to estimate the biological relevance of the alteration in DAT density when compared with the alteration in serotonin transporter density, since there are no published data about the findings on other monoamine transporters (than DAT) in depression. Since the ventral part of the striatum belongs to the limbic system, it would have relevant to study DAT especially in this area (nucleus accumbens), but that was not possible due to the limits of resolution.

### 6.2.2. The up-regulation of DAT density

In SPECT scans taken 21-24 hours following injection, we found a significantly higher [$^{123}$I]β-CIT uptake in patients with major depression than in the controls. This finding may reflect a higher striatal dopamine transporter density rather than mere perfusion, since the equilibrium between receptors and free ligands had been achieved at 21-24 hours. Our finding on DAT density was surprising, since one would expect that lower dopamine transmission would lead to secondary down-regulation of DAT density. However, it is possible that up-regulation of the DAT may be the primary alteration, which leads to a lower intrasynaptic dopamine concentration and to lower dopamine neural transmission. This may also lead to secondary compensatory up-regulation of postsynaptic $D_2$-receptor density, as observed in the IBZM study (Shah et al. 1997). Another explanation for the IBZM findings is a lower intrasynaptic dopamine concentration (which competes with the ligand when occupying the receptors), leading to higher IBZM ligand uptake.

### 6.2.3. Comparison of studies on DAT density in major depression

Brunswick et al. (2003) found also increased DAT availability in the right anterior putamen, the right and left posterior putamen and the left caudatum in depressed patients compared with healthy controls. Their findings were in line with our findings. They studied 15 depressed patients (nine men, six women) with a mean age of 40 ± 12 years. The mean HRSD was 22 ± 4. The diagnoses varied from major depression (n = 10) to type II bipolar depression (n = 5). A common factor in both these studies is a slight psychomotor retardation, which could be related to the increased DAT specific uptake values.

Neumeister et al. (2001) reported opposite findings when they studied DAT availability in symptomatic depressed patients with seasonal affective disorder (SAD) and healthy controls. They studied eleven drug-free depressed patients with SAD and eleven healthy age- and gender-matched controls. The diagnoses were carried out with methods similar to ours with the exception of using the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD). One explanation for the discrepancy between this and our study may come from differences between the groups of patients.

### 6.2.4. Gender, age and DAT

Pohjalainen et al. (1998) have reported that there might be sex differences in the striatal $D_2$-receptor density. Their study revealed lower $D_2$-receptor affinity and a higher concentration of endogenous striatal dopamine in women (Pohjalainen et al. 1998). Staley et al. (2001) observed a higher striatal DAT availability in women than in men. In a study by van Dyck et al. (2002a), the age-related decline in striatal [$^{123}$I]β-CIT binding was 6.6% per decade. In our study the patients and controls did not differ significantly in age and gender. However, to avoid such a gender effect, we adjusted our data for age and sex.

### 6.2.5. Strengths and limitations

Strengths of our study were that our patients were drug-naive, all the patients had current major depression without any other comorbid diagnoses and that the patients and controls did not differ significantly in age or gender. The limitation was the small sample size (n=15).

## 6.3. Effect of cluster C personality disorder on striatal DAT densities in major depression (III)

Our findings suggest that despite the fact that personality disorders in general affect the clinical manifestation of depression, cluster C personality disorder has no independent effect on DA transmission as reflected by DAT density. We demonstrated that if the clinical status is controlled for, cluster C PD has only a small effect (effect size <0.3) on DAT levels when compared to the effect of depression (effect size = 1.44). Both depression groups (with or without cluster C PD) differed from the control group. The DAT densities among depressed patients were higher than those in the control group, which was in line with our previous study (II).

In an earlier study on 18 healthy subjects, low dopaminergic neurotransmission associated with a detached personality when using correlation analysis (Laakso et al. 2000). Our results and this finding are difficult to compare, because Laakso et al. (2000) used healthy volunteers. Furthermore, their personality status was assessed by self-report questionnaire. Personality disorders cannot exist in healthy subjects, but instead there will be a continuum of personality features.

### 6.3.1. Strengths and limitations

A strength of our study was the inclusion of an adequate diagnostic procedure. The effect of affect state could also be controlled for in our study. One limitation of this study was the relatively small sample size, so we could not entirely exclude the possibility of Type 2 statistical errors (Wassertheil-Smoller 1995).

## 6.4. [$^{123}$I]β-CIT binding and recovery from depression (IV)

We made a longitudinal comparison of patients before and after recovery from depression during six months of follow-up and found that the patients who recovered had a significantly greater increase in [$^{123}$I]β-CIT binding in the midbrain than non-recovered patients. This might imply that SERT density in the midbrain increases during recovery from depression. If our patients had had more severe depression it might have caused a more notable difference in [$^{123}$I]β-CIT binding between recovery and non-recovery groups. We did not find significant differences in the striatal DAT densities between responders and non-responders.

We found that in those patients who did not recover from depression during the six months of treatment, [$^{123}$I]β-CIT binding remained at the same level or even decreased. According to Malison et al. (1998), the decrease in SERT density in depression may be a consequence of transporter downregulation, which may result from: 1) a marker for a primary, perhaps etiologic defect in the development or functioning of the 5-HT system, or both, 2) an adaptive, perhaps compensatory attempt by neurons to overcome another etiologic factor, or 3) an unrelated and perhaps secondary sequela of another primary, etiologic lesion. Malison et al. (1998) concluded that the decrease in SERT density may be due to an increased level of extracellular 5-HT. However, this conclusion was based on a cross-sectional study.

According to our findings, we suggest that the up-regulation of DAT may be the primary alteration, which leads to a lower intrasynaptic dopamine concentration and lower striatal dopaminergic neurotransmission. However, the results of our study, together with those of Malison et al. (1998), suggest that depression is associated with a decrease in SERT density in the midbrain. This finding was in line with Willeit et al. (2000), who also found a decreased SERT density in thalamus-hypothalamus region in depressed patients with SAD. Dahlström et al. (2000) reported opposite findings with children and adolescent patients with depression. They found increased SERT availability in the hypothalamus/midbrain region in depressed patients compared with healthy controls. A limitation of their study was that they did not have age- and gender-matched controls. The main explanation for the discrepancy

between that and our study was that the study groups differed significantly in age, and that depression in children may differ clearly from depression in adults. The major limitation of these studies was that they were cross-sectional and thus had no follow-up.

### 6.4.1. Medication

Our patients had received no antidepressant medication before the first SPECT scan, and three patients treated with antidepressants during the follow-up had at least a one-month drug-free period before the second SPECT scan. We postulate that this arrangement minimized the influence of antidepressant medication on tracer uptake, although the influence of longterm antidepressant medication remains unknown. In this study we did not analyze treatment associations because our study design was observational and therefore there is always a possible two-way process; undertreatment may lead to a worse clinical state, or a worse clinical state may lead to more treatment.

### 6.4.2. Strengths and limitations

When considering our sample size (n = 18), the use of the median HRSD as a means of differentiating responders and non-responders was appropriate. However, the use two different methods when dividing the groups results in similar findings. This was a strength. One limitation of this study was the small sample size, so we could not totally exclude the possibility of Type 2 statistical errors.

# 7 SUMMARY

The results of our benzodiazepine receptor study were in line with the results from previous studies on panic disorder patients. Ours was the first published study concerning the benzodiazepine receptor density in major depression. In the future our results need to be replicated.

Our hypothesis regarding the lower density of DAT in depression was formed on the basis of the assumption that decreased dopamine function would secondarily lower DAT density (down-regulation). However, our results suggest that, at least for this subgroup of depressed patients, the primary dysfunction in the dopaminergic system may be the up-regulation of DAT density, which results in a more effective re-uptake of dopamine into the presynaptic neurons. This leads to a lower concentration of dopamine in the synaptic cleft and thus causes a reduction in dopaminergic neurotransmission. The neurobiological etiology of depression is heterogenous. Further studies should exam the DAT density in greater detail using a larger number of patients with different kinds of clinical symptoms.

Our results are the first to suggest that cluster C PD has no independent effect on dopaminergic neurotransmission in the striatum. Cluster C PD represents self-opinion and attitudes and it does not manifest itself only in behavior. However, our results need to be replicated in a larger group. While depression is associated with increased DAT density, cluster C PD alone is not necessarily associated with DAT densities. Our results indicate that DAT density in depression is higher than DAT density in healthy controls, independent of whether there is comorbidity with cluster C personality disorder.

Although we did not detect differences in striatal DAT density between the responders and the non-responders in the recovery study, we found increased SERT density in the midbrain of the recovered patients. Because monoamine pathways are closely related, we assume that recovery from depression may be associated with both dopaminergic and serotonergic neurotransmission.

The studies of CBF and metabolism of the brain do not provide any information about the neuropharmacological etiology of depression, as transmitter specific studies do. The neurobiological etiology of depression underlines the importance of transmitter specific studies, because they can give us useful information about neuropharmacological functions of the brain. Better understanding of these functions aids in executing the pharmacological treatment of depression.

# 8 CONCLUSIONS AND FUTURE RECOMMENDATIONS

Depression is associated with increased striatal DAT density, which may lead to a lower intrasynaptic dopamine concentration and lower dopamine neural transmission.

Cluster C PD has no independent effect on DA transmission as reflected by DAT density.

Recovered depressed patients have higher [$^{123}$I]β-CIT binding in the midbrain than when in the depressed state. This is not found among non-recovered depressed patients.

A 6-month follow-up revealed increased SERT densities in clinically improved patients, and vice versa, suggesting that SERT density may be, at least partly, a state dependent variable, which is a finding not reported before.

Further studies are needed with prospective assessments and with larger study groups from the general population in order to avoid selection bias.

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# ORIGINAL PUBLICATIONS
# I - IV

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