International Journal of Neuropsychopharmacology (2001), **4**, 21–31.

Basal limbic system alteration in major depression: a hypothesis supported by transcranial sonography and MRI findings

Georg Becker[1], Daniela Berg[1], Klaus Peter Lesch[3] and Thomas Becker[2]

[1] *Neurologische Universitätsklinik Würzburg, Germany*
[2] *Psychiatrische Universitätsklinik Leipzig, Germany*
[3] *Klinik für Psychiatrie und Psychotherapie, Universität Würzburg, Germany*

Abstract

The pathogenesis of major depression (MD) remains unclear despite intensive research in the last decades which brought up a multitude of findings illustrating the complexity of this disorder. In this paper we will summarize the evidence pointing towards a structural alteration of the basal limbic system in MD and depression in Parkinson's disease (PD). Transcranial ultrasound and MRI studies in both depressive syndromes revealed altered signal intensity of the brainstem midline comprising fibre tracts of the basal limbic system. The hypothesis of a structural disruption of the basal limbic system is supported by biochemical and histopathological findings. The similarity of findings in MD and depression in PD might reflect a relationship between MD and neurodegenerative disorders.

Received 16 April 2000; Reviewed 24 July 2000; Revised 16 November 2000; Accepted 19 November 2000

Key words: Major depression, affective disorders, limbic system, Parkinson's disease, transcranial ultrasound.

Introduction

Over the last decades basic research and clinical studies have increased our knowledge of the pathogenesis of major depression (MD). Social and psychological factors are considered important, but organic aspects are also confirmed by various lines of evidence. Neuroimaging, for example, has disclosed a huge battery of abnormalities in MD, such as reduced volume (Coffey et al., 1993; Husain et al., 1991; Jetste et al., 1988; Krishnan et al., 1992), hypometabolism (Baxter et al., 1989; Buchsbaum et al., 1986; Martinot et al., 1990) and a reduced blood flow (Bench et al., 1992, 1995; Ebert et al., 1991; Ito et al., 1996; Mayberg et al., 1994; Rubin et al., 1995) of specific brain areas, particularly the frontal lobe and the basal ganglia. In addition, basic research has provided compelling evidence regarding the alteration of the noradrenergic, dopaminergic, and serotonergic systems (Ball and Whybrow, 1993). Monoamines have been found to be depleted (Goodwin et al., 1973; Joyce and Paykel, 1989; Leonard, 1997; Papeschi and McClure, 1971; van Praag and Korf, 1975; Schildkraut, 1973), related receptors are altered with respect to their density (Biver et al., 1997; Drevets et al., 1999; Garcia-Sevilla et al., 1999; Larisch et al., 1997; Sastre and Garcia-Sevilla, 1997; Yatham et al., 1999), and recent evidence suggests a mismatch of receptor-coupled signal transduction in MD (Avissar et al., 1997; Duman et al., 1997; Garcia-Sevilla et al., 1999; Shelton et al., 1996). Genetic studies have demonstrated an association between several transporter or receptor genes and MD (Collier et al., 1996; Gutierrez et al., 1998; Lesch and Mössner, 1998; Manki et al., 1996; Ogilvie et al., 1996; Oruc et al., 1997). However, the definite relation between the gene products and mood disorder remains obscure. Even this condensed summary of data illustrates the complexity of biological findings in this disorder.

In this paper we will summarize evidence pointing towards the basal limbic system being affected in primary and secondary depression. This hypothesis derives primarily from neuroimaging research, particularly transcranial sonography. Transcranial sonography (TCS) is a new diagnostic tool allowing the 2-D visualization of brain parenchyma through the intact skull. Accumulation of evidence indicates that TCS may complement magnetic resonance imaging (MRI) data (Becker et al., 1995b, 1999; Berg et al., 1999a; Naumann et al., 1996) and may provide new insights into the diagnosis and pathogenesis of psychiatric disorders.

Address for correspondence: Dr G. Becker, Department of Neurology, University of Würzburg, Josef-Schneider-Str. 11, 97080 Würzburg, Germany.
Tel.: ++ 49 931 2012621 *Fax*: ++ 49 931 2013489
E-mail: georg.becker@mail.uni-wuerzburg.de

Basic application of TCS

TCS is performed using modern colour-coded Duplex ultrasound systems equipped with a 2.0–2.5 MHz phased array transducer (Becker and Griewing, 1998). Low probe frequencies are required to scan through the intact skull. Bone windows suitable for transcranial examination can be found at the temporal squama right in front of the ear. These temporal bone windows are well known from conventional transcranial Doppler sonography. Sonographic identification of the brain parenchyma through the narrow acoustic bone window requires tilting and rotating of the probe (Figure 1). This results in oblique scanning planes which make initial anatomic orientation difficult.

TCS examination starts with the patient lying in supine position and the ultrasound probe pressed firmly at the temporal bone window. Ultrasound examination is usually started in the axial plane (orbito-meatal line) by visualizing the mesencephalic brainstem (Figure 1) and subsequently tilting the probe to visualize more apical brain stuctures. The ultrasound pattern of the brain structures depends on the tissue impedance and tissue propagation velocity of the ultrasound but also on factors which vary individually, e.g. the quality of the temporal bone window. Most areas of the brain parenchyma exhibit a low echogenicity but certain factors may substantially increase tissue echogenicity including calcium deposits (e.g. basal ganglia calcification), increased cell count (e.g. brain tumours) or heavy metal inclusions. Despite a high axial resolution, the contrast resolution of transcranial ultrasound is inferior compared with CT and MRI. On TCS imaging one can easily identify structures of the midline, such as the ventricular system (Figure 1),

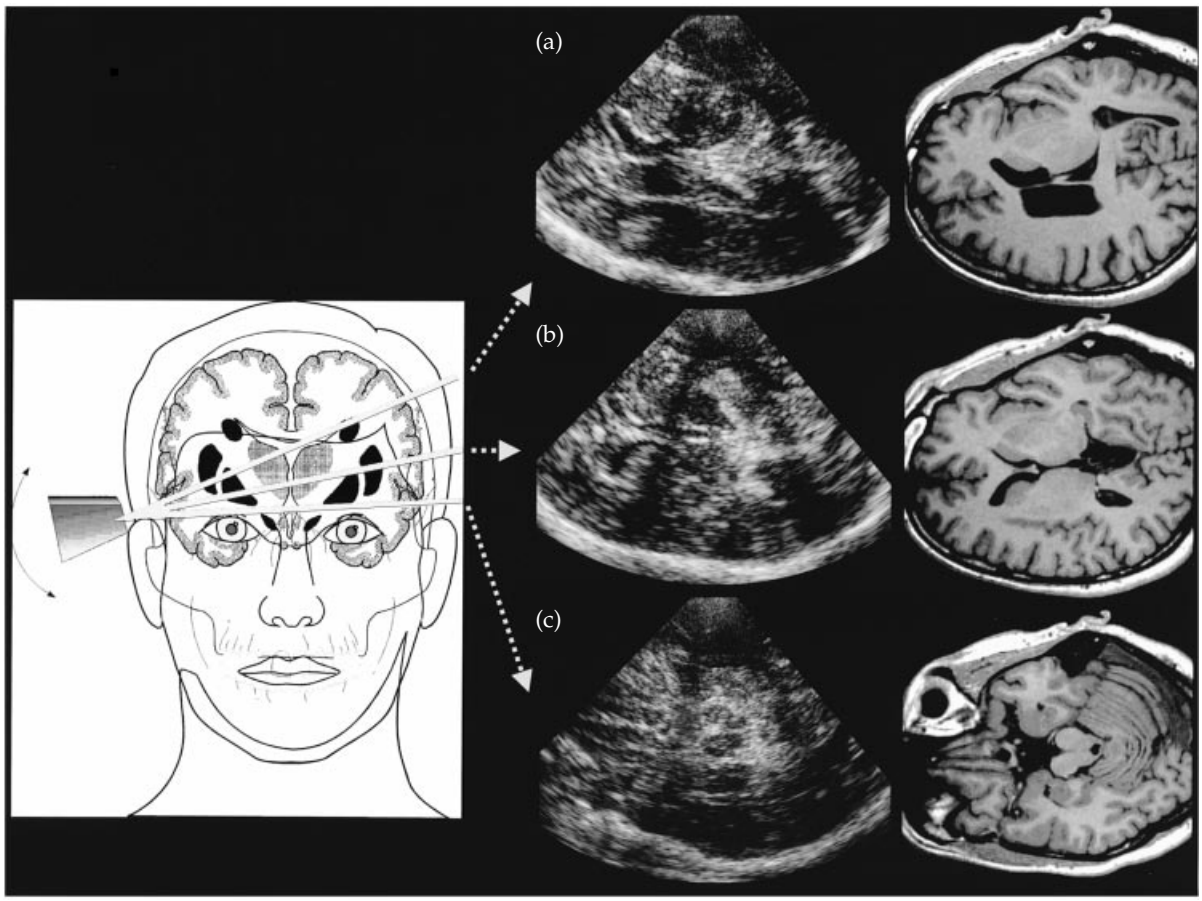

Figure 1. Schematic illustration of the sonographic examination of the brain through the temporal acoustic bone window. Diverse brain structures may be detected with transcranial sonography by tilting and rotating the probe on the temporal bone window. Three standardized axial scanning planes have been described which are illustrated in comparison to MRI slices. (c) Mesencephalic slice (see also Figure 2). (b) Diencephalic slice demonstrating the 3rd ventricle and the frontal horns of the lateral ventricles. (a) Cella media slice demonstrating the body of the lateral ventricles. The scanning angle and orientation of MRI slices were adapted to TCS slices to allow easier anatomical orientation.

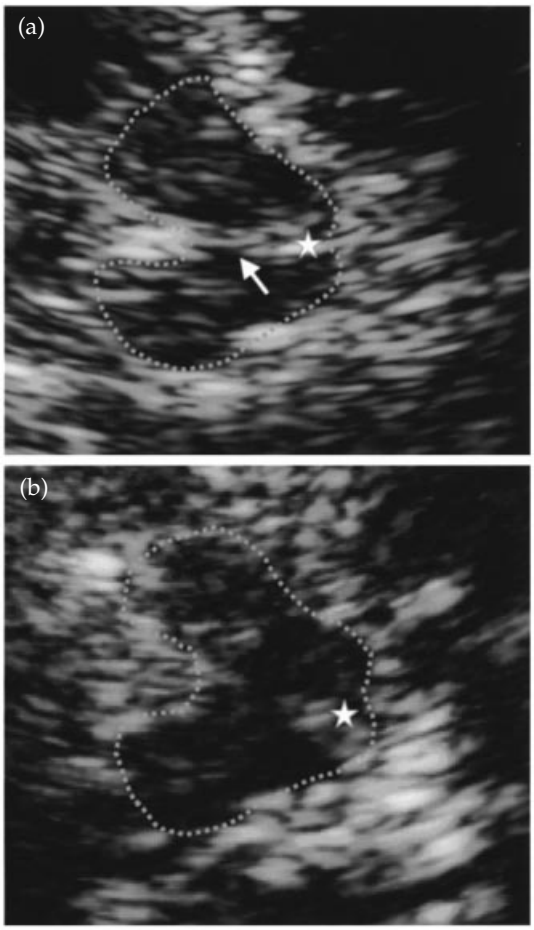

Figure 2. Ultrasound images of the mesencephalic brainstem. (a) Ultrasound findings in a normal adult illustrate an echogenic butterfly-shaped mesencephalic brainstem which is surrounded by the hyperechogenic basal cisterns. At the midline a sagittal running hyperechogenic band (➔) can be detected, dividing the brainstem and representing the brainstem midline (raphe); ★, aqueduct. (b) Ultrasound findings of a patient with major depression; at the midline of the mesencephalic brainstem no hyperechogenic band can be identified despite unequivocal detection of other structures like the aqueduct (★).

but a differentiation of grey and white matter or the identification of diencephalic nuclei is not feasible. In contrast, the axial resolution of TCS in the focus zone is 0.7 mm and therefore well in the range known from CT and MRI.

Ultrasound studies in affective disorders focused primarily on the ultrasound pattern of the brainstem. The mesencephalic brainstem emerges as a butterfly-shaped structure of low echogenicity (Bogdahn et al., 1990; Puls et al., 2000). It is surrounded by the hyperechogenic basal cisterns and more laterally and dorsally by the temporal lobes and the cerebellum which also exhibit low echogenicity (Figure 2a). Typically, a hyperechogenic lining at the midline of the mesencephalic and pontine brainstem can be identified, extending in an anterior–posterior (a.p.) direction from the anterior surface of the brainstem to the aqueduct (Figure 2a). The lateral extension of this hyperechogenic structure is about 1–2 mm, and therefore this hyperechogenic area encompasses the anatomical structure of the 'brainstem raphe'. The term raphe describes structures at the midline of the brainstem including pathways and nuclei, e.g. the raphe nuclei (for details see below). Approx. 90% of healthy volunteers exhibit a moderately to distinctly hyperechogenic midline structure at the ponto-mesencephalic brainstem (Becker et al., 1994, 1995a; Puls et al., 2000). Sometimes hyperechogenic signals at the midline are interspersed with hypoechogenic signals so that it is usually less than the complete a.p. extension of the midline which exhibits increased echogenicity leading to a dotted hyperechogenic line on TCS. A low echogenicity of the brainstem midline identical to that of the adjacent brain parenchyma is detected in about 10% of healthy subjects, i.e. a brainstem midline (raphe) is not visible on TCS (Becker et al., 1994, 1995a; Puls et al., 2000). Dorsally the hyperechogenic brainstem midline is bordered by the circular echogenic structure of the aqueduct (Figure 2a). At the base of the brainstem peduncles the echogenic shell of the red nucleus can sometimes be depicted. By tilting the scanning plane more upwards diencephalic and parietal brain structures can be detected (Figure 1). Ultrasound features of these areas are described in detail elsewhere (Becker and Griewing, 1998).

The assessment of the brightness (echogenicity) of the brainstem midline (raphe) or every other structure of the brain or other organs leads to a fundamental problem of diagnostic ultrasound. The echogenicity of a structure depends on many factors including tissue impedance, the quality of the bone window, and ultrasound system adjustment. Since the absolute brightness or echogenicity is not measurable in a standardized mode we proposed to quantify echogenicity of a structure using a semi-quantitative grading in relation to adjacent structures. The echogenicity of the brainstem midline (raphe) was rated in relation to the echogenicity of the brainstem tectum. When this type of assessment was performed by two experienced ultrasound physicians the reproducibility of echogenicity ratings was sufficient (weighted kappa 0.7; Becker et al., 1997). The fact that the ultrasound signal intensity is not quantifiable concerns all sorts of sonographic applications and all diagnostic field of ultrasound (echocardiography, abdominal sonography). On the other hand, diagnostic ultrasound has proven to be both a valuable and reliable diagnostic instrument despite the

immanent limitation of semi-quantitative measurements of signal intensity.

Ultrasound findings in major depression

A pilot study on patients with MD drew our attention to the brainstem midline (raphe), an anatomical area comprising fibre tracts of the basal limbic system. In this study we examined 20 patients with unipolar depression and compared the echogenicity of several brain areas including the midline of the brainstem with 20 age- and sex-matched healthy volunteers (Becker et al., 1994). The echogenicity of the brainstem midline was found to be significantly reduced in patients with MD compared to controls (Figure 2b). While in 17 of the 20 patients with MD the brainstem midline (raphe) was not visible because the brainstem midline exhibited almost no hyperechogenic signal, lack of visualization did not occur in healthy volunteers.

These findings were confirmed in a consecutive study including 40 patients with MD. TCS findings of the brainstem midline were compared with those of 40 healthy controls, 40 patients with a bipolar disorder and 40 patients with schizophrenia (Becker et al., 1995a). Ultrasound examinations were performed after the acute psychiatric symptoms had subsided. The echogenicity of the brainstem midline was significantly lower in MD than in the other groups. Hyperechogenic signal at the midline was lacking in 27 patients with MD but only in 1 patient with a bipolar disorder, and in 2 patients with schizophrenia. The visibility of the brainstem midline on TCS did not correlate with the age or sex of the individuals included in this study. Furthermore, no correlation between the severity of depressive symptoms at the time of TCS examination and the echogenicity of the brainstem midline was identified. Follow-up studies revealed no change in echogenicity during a time-course of 3 months.

What is the likely cause for this replicable and consistent TCS finding? Experience with ultrasound in the last 50 years revealed that a shift in tissue echogenicity reflects a change in tissue impedance and points towards an alteration of the tissue microarchitecture. This may be caused by a modification of tissue cell density, the interstitial matrix composition or an alteration of fibre tract integrity. Ultrasound findings therefore strongly indicate structural pathology involving the midline structures of the brainstem in patients with MD.

Ultrasound findings in secondary depression

In two consecutive studies we performed TCS examinations of depressed and non-depressed PD patients comparing the echo-patterns of the brainstem midline. Both studies included a total of 61 PD patients (Becker et al., 1997; Berg et al., 1999b). Thirty-three PD patients fulfilled the diagnostic criteria of an affective disorder in concomitant medical disorder (DSM-IV, 293.83) and 28 were not depressed. In 19 of the 33 depressed PD patients the brainstem midline (raphe) was not visible, i.e. no hyperechogenic signals were detected at the midline of the brainstem. The same was observed in only 2 of the 28 non-depressed PD patients. The echogenicity of the brainstem midline was not influenced by the age or sex of the patients nor by the severity of depressive symptoms or current antidepressant medication.

These findings indicate that depressed PD patients exhibit the same ultrasound feature as patients with MD. Analogous ultrasound findings have been identified in patients with dystonia and depression (Naumann et al., 1996) and in a small group of patients with Huntington's disease and depression (Becker G. et al., unpublished observations). Interestingly, no reduction or loss of echogenicity of the brainstem midline was found in depressed patients with multiple sclerosis (Berg et al., 2000). The similarity of ultrasound findings in MD patients and depressed PD patients supports the notion of a common pathomorphological basis in both forms of depressive illness which is not seen in inflammatory demyelinating disease.

MRI findings of the brainstem raphe in primary and secondary depression

The consistent way in which TCS illustrates abnormalities of the brainstem raises the question of whether this finding can be reproduced using MRI. In a retrospective study we analysed the signal intensity of the brainstem midline in MD (Becker et al., 1998). The study included MRI scans of 140 controls, 19 patients with MD and 12 patients with a bipolar disorder. Semi-quantitative assessment of T2-weighted MR images revealed that the signal intensity at the brainstem midline was significantly increased in MD patients compared with controls and patients with bipolar disorders.

Similar to primary depression alterations of the brainstem were also seen in patients with secondary depression. This has been shown by a prospective MRI study comparing MRI features of depressed and non-depressed PD patients (Berg et al., 1999b). According to a semi-quantitative assessment and quantitative measurements of the T2 relaxation time, depressed PD patients exhibited a shift of signal intensity at the brainstem midline of the mesencephalon (Berg et al., 1999b). Signal intensity was independent of the current severity of the depressive symptoms. In contrast, patients with multiple sclerosis and depression showed no abnormalities of the brainstem signal intensity on MRI (Berg et al., 2000).

The data indicate that MRI, like TCS, points towards a structural alteration of brain tissue in the midline of the mesencephalon in patients with MD or depressed patients with PD. This contrasts with findings in depression associated with multiple sclerosis where no change of the TCS and MRI features of the brainstem midline (raphe) was observed (Berg et al., 2000). An increase in the signal intensity of the brainstem midline (raphe) on T2-weighted images may be evoked, e.g. by a myelin breakdown of pathways running through the brainstem midline. A disruption of sagittally running fibre tracts at the midline of the brainstem would also explain the reduced echogenicity on TCS because this results in a lack of structures reflecting the insonated ultrasound beam. Therefore, a reduced signal intensity on TCS and an increased signal intensity on MRI might be two reflections of the same pathopysiological process emphasizing a structural alteration of the brainstem in depression.

Neuroanatomical correlates of the brainstem raphe

The area of hyperechogenic signal at the midline of the mesencephalic and upper pontine brainstem detected by TCS extends from the anterior surface of the brainstem to the aqueduct in an a.p. direction with a lateral extension of about 1–2 mm comprising several pathways and nuclei of the rostral brainstem. The main fibre complex constituting this area is the medial forebrain bundle, but other pathways also run through the midline of the upper brainstem, such as the longitudinal fasciculus of Schütz, the tractus mamillotegmentalis, the fasciculus retroflexus, and crossing fibre tracts from the cerebellum (Carpenter and Sutin, 1993; Geyer et al., 1976; Glowinski et al., 1984; Holstege, 1990; Lang, 1993; Niewenhuys, 1985). These fibre tracts connect bidirectionally diverse brainstem and cerebellar nuclei (raphe nuclei, interpeduncular nuclei, ventral and dorsal tegmental area, central grey, central superior nucleus) with subcortical nuclei (hypothalamus, basal ganglia, thalamus, habenula, mamillary bodies, septal and preoptical region) and cortical areas, particularly in the frontal cortex. These pathways are central components of the limbic network constituting the basal limbic system. Numerous studies have emphasized the role of the basal limbic system and its related brainstem nuclei in the regulation of mood, emotions, behaviour, sleep, reinforcement mechanisms, and locomotion (Hillegaart, 1991; Inglis and Winn, 1995; Jones B, 1991; Jones SL, 1991; Kitayama, 1997; Mann, 1999; Pratt, 1992; Sawynok et al., 1995; Simpson and Weiss, 1988; Stevens and Livermore, 1978; Weiss et al., 1994; Willick and Kokkinidis, 1995; Yavari et al., 1993). A change of the raphe signal detected by TCS and MRI, therefore, could suggest an impairment of the basal limbic system in depression.

Preliminary histopathological evidence for a basal limbic system disruption in MD

There are only a few neuropathological studies on major depression, some of which do not focus primarily on depression and include heterogeneous types of affective disorders. None of these studies have revealed consistent neuropathological abnormalities in any of the various brain areas examined (Jeste et al., 1988). None of these studies, however, performed a neuropathological examination of the brainstem and its nuclei. Recently, Baumann and co-workers have reported on a reduced cell count of the raphe nuclei in major depression (Baumann et al.,

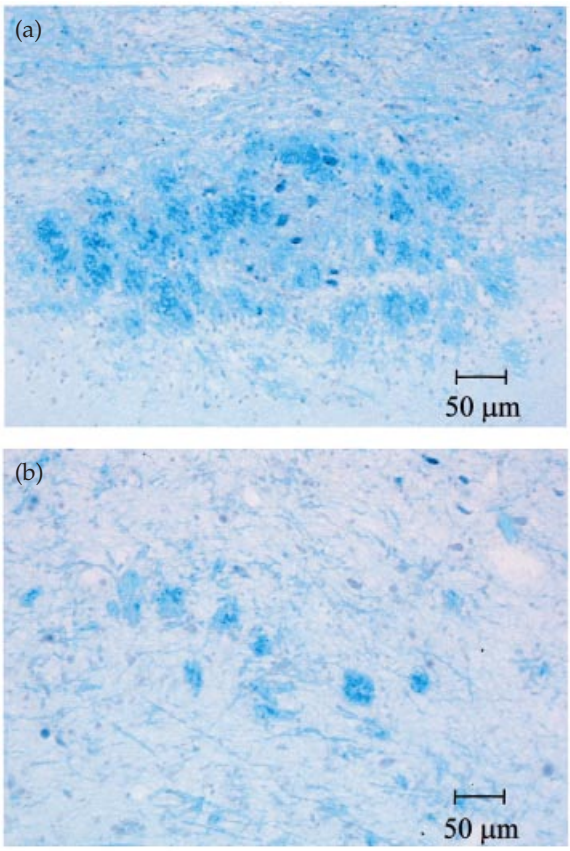

Figure 3. Histological findings of the brainstem midline (raphe) (sagittal section through the midline of the potomesencephalic brainstem). (a) Myelin staining (Klüver–Barera) in normal adults illustrate bundles of crossing fibres at the midline of the pontine brainstem (fibrae arcuatae). (b) Same area in a patients with unipolar depression; a substantial rarefaction of crossing fibre tracts can be detected.

Table 1. Cause of deaths and post-mortem delay of 2 patients with major depression, 2 patients with bipolar disorders and 5 controls (Senitz, personal communication: June 1999)

	Major depression	Bipolar depression	Controls
No. of patients	2	2	5
Sex (no. of patients)	Female (1), male (1)	Female (2)	Female (1), male (4)
Post-mortem delay	33 ± 4 h	33 ± 4 h	39 ± 12 h
Cause of death	Myocardiac infarction (1), pulmonary embolism (1)	Pulmonary embolism (2)	Myocardiac infarction (3), pulmonary embolism (2), cardiac failure (1)
Staining methods	HE staining, Nissl-staining, reduced silver staining (Palmgren), PAS staining, myelin staining (Klüver–Barera)		

Histopathological analysis of the midline structures of the brainstem was performed on the standardized sagittal section of the brainstem using the staining method listed in the table.

1998). In addition, the same group has determined a significant cell count reduction of pigmented neurons in the locus coeruleus in MD patients when compared with patients suffering from bipolar disorder (Baumann et al., 1999). Comparison with controls revealed a decrease in cell count which, however, did not reach the level of significance presumably due to the relatively low number of patients included. Locus coeruleus neurons have been also reported to be reduced in suicide victims (Arango et al., 1996). Furthermore, Klimek et al. (1997) have shown reduced norepinephrine transporter concentrations in the locus coeruleus of patients with MD; however, the number of pigmented neurons remains unaffected.

Recent findings from one of our departments (Senitz, personal communication: June 1999) are in line with this data. Comparison of the histopathology of the brainstem of 2 patients with definite MD, 2 patients with a bipolar disorder and 5 control patients considered specifically the fibre tracts at the midline of the brainstem (Figure 3). Sex, age, cause of death, post-mortem delay of the patients and histopathological methods used are outlined in Table 1. Patients with MD showed a distinct disruption of fibre tracts passing the mesencephalic midline (raphe). These preliminary data may shed light on factors leading to a shift of signal intensity at the mesencephalic midline (raphe) as defined by TCS and MRI.

Hypothesis of an alteration of the basal limbic system in primary and secondary depression

Genetic susceptibility factors have been identified to play an important role in the aetiology of affective illness including bipolar affective disorder and unipolar depression (Collier et al., 1996, Gutierrez et al., 1998; Lesch and Mössner, 1998; Manki et al., 1996; Ogilvie et al., 1996; Oruc et al., 1997). Heritability is estimated to be up to 86% for bipolar disorder and 30–37% for unipolar depression (Craddock and Jones, 1999; Kendler et al., 1999). Although both disorders may share factors which determine depressive symptomatology with an associated high risk of suicide, genetic heterogeneity and substantial but varying environmental and endogenous components complicate identification of predisposing genes. According to our findings we hypothesized a disruption of the basal limbic system to be *one* factor in the development of MD and certain forms of secondary depression. This hypothesis is in line with various biochemical, histopathological, pharmacological, and neuroimaging findings.

A vast body of evidence implicates the noradrenergic, serotonergic, and dopaminergic system in the pathogenesis of depression (for a review see Ball and Wybrow, 1993). This evidence derives from various sources, particularly from research on the mechanism of the action of antidepressant drugs. The basal limbic system encompasses noradrenergic nuclei (locus coeruleus), serotonergic nuclei (the raphe complex), and dopaminergic nuclei (e.g. ventral tegmental nucleus). An impairment of the basal limbic system would therefore inevitably result in a reduction of these monoaminergic transmitters and their metabolites as shown by many neurochemical studies in primary depression (Goodwin et al., 1973; Joyce and Paykel, 1989; Leonard, 1997; Molchan et al., 1991; Papeschi and McClure, 1971; van Praag et al., 1973; van Praag and Korf, 1975; Schildkraut, 1973; Staley et al., 1998; Syvalahti, 1987). The relevance of the serotonergic neurotransmission for the regulation of mood has been outlined. Serotonin influences many physiological functions including motor activity, food intake, sleep, reproductive activity, endocrine rhythms as well as emotion and anxiety (Mössner et al., In Press). It has been realized that a certain allelic variation of the 5-HT transporter gene expression is associated with an increased

risk for depression (Collier et al., 1996). Similar findings have been reported in PD and depression. The type of 5-HT transporter gene expression represents an important risk factor for the development of anxiety and depression in PD (Menza et al., 1999; Mössner et al., In Press). These findings underline the central role of serotonin neurotransmission in the pathogenesis of primary and secondary mood disorders.

Further evidence for an injury of brain areas associated with the basal limbic system comes from neuroimaging findings. PET and SPECT studies in MD patients have determined a hypometabolism and reduced blood flow mainly of the frontal lobe and basal ganglia (Baxter et al., 1989; Bench et al., 1992, 1995; Buchsbaum et al., 1986; Ito et al., 1996; Ebert et al., 1991; Martinot et al., 1990; Mayberg et al., 1994; Rubin et al., 1995). The frontal lobe and basal ganglia are known to be important projection areas of the basal limbic system particularly of the medial forebrain bundle. Recent SPECT and PET ligand imaging have demonstrated decreased serotonin transporter availability and a reduced serotonin$_{1A}$ receptor binding potential in the midbrain raphe of patients with MD, two findings in accordance with TCS and MRI findings illustrating lesions of the same structure (Drevets et al., 1999; Malison et al., 1998). Volumetric measurements of different brain areas have revealed inconsistent and miscellaneous results. While many studies agree on the finding of a ventricular and sulcal enlargement some observed a reduced volume of the basal ganglia, the frontal and temporal lobe, but also of the brainstem and the cerebellum (Coffey et al., 1993; Husain et al., 1991; Jeste et al., 1988; Krishnan et al., 1992; Shah et al., 1992). MR spectroscopy studies have reported lower levels of nucleoside triphosphate in the basal ganglia of unmedicated MD patients (Moore et al., 1997). In combination with findings of a decreased choline level (Renshaw et al., 1997) and PET data (Baxter et al., 1985; Buchsbaum et al., 1986) this may reflect a reduced metabolism in the basal ganglia in MD. In summary, these findings suggest an impairment of core structures associated with the basal limbic system.

The similarity of ultrasound findings in MD and depression in PD suggests a common pathogenetic basis of both depressive disorders. Looking at biochemical and neuroimaging data in depressed PD patients various similarities of both phenotypes of depression occur. Low concentrations of norepinephrine, serotonin, and dopamine, or their metabolites have been found in the CSF of depressed PD patients (Asberg et al., 1984; Brücke et al., 1984; Kienzl et al., 1990; Kostic et al., 1987; Mayeux et al., 1986, 1988; Roy et al., 1985; Sano et al., 1989). In addition, nuclear medicine studies revealed a reduced glucose metabolism and cortical blood flow at the frontal cortex (Mayberg et al., 1990; Ring et al., 1994), matching findings reported in MD. In comparison to MD, however, the PD literature supplies us with two examples of histopathological data evaluating the role of brainstem nuclei in PD and depression. Paulus and Jellinger (1991) have reported on an increased neuronal loss in the serotonergic raphe complex of depressed PD patients which was well beyond the edge of nerve cell reduction observed in non-depressed PD patients. Likewise pigmented neurons in the ventral tegmental nucleus have been found to be reduced more markedly in brains of depressed vs. non-depressed demented PD patients (Torack and Morris, 1988), which corroborates Fibiger's hypothesis that the dopaminergic mesolimbic–mesocortical projections contribute to the high incidence of depression in PD (Fibiger, 1984). Further morphological evidence comes from the findings of cell loss in the noradrenergic locus coeruleus in demented PD patients with depression (Chan-Palay and Asan, 1989). Similar to biochemical and neuroimaging studies these findings correspond to preliminary data observed in MD. In summary, brainstem nuclei of the basal limbic system show a reduced cell count in depressed PD patients which may affect pathways originating from these nuclei passing through the midline of the brainstem. Altered echogenicity/signal intensity of the brainstem midline (raphe) comprising these pathways as demonstrated by TCS and MRI could reflect such change.

Conclusion

Findings of various sources demonstrate that the basal limbic system may play a role in the pathogenesis of depression. Ultrasound and MRI display an impairment of the brainstem midline (raphe) at which pathways of the basal limbic system are assembled. Meanwhile, preliminary histopathological studies indicate an impairment of nuclei associated with the basal limbic system. Analysis of data obtained in MD and depression in PD discloses similarities of both depressive syndromes in many respects considering clinical, biochemical, neuroimaging, and histopathological findings. The analogy may suggest a common basis for both types of depression and implies a relation between MD and neurodegenerative disorders. The nature and cause of basal limbic disruption remain unclear. In addition, the findings presented allow no conclusion as to whether abnormalities are primary or whether they reflect a secondary phenomenon due to some other, hitherto undefined process. However, it should be pointed out that the alteration of the basal limbic system as detected by neuroimaging is considered only *one* of several factors in the pathogenesis of depressive illness because not all patients with MD show

altered signal intensity of the brainstem midline (raphe) and because ultrasound findings typical of patients with depression may be also detected in some healthy subjects.

Acknowledgements

The authors thank Professor Klaus Lange for the critical review of the manuscript. We also acknowledge the help of Dr Senitz (Department of Psychiatry, Würzburg), who performed the histological studies of depressive patients. In addition, we thank Dr Lindenlaub for technical assistance in the preparation of the manuscript. This study was supported by research grants from Siemens AG, Germany,

References

Arango V, Underwood MD, Mann JJ (1996). Fewer pigmented locus coeruleus neurons in suicide victims: preliminary results. *Biological Psychiatry 39*, 112–120.

Asberg M, Bertilsson L, Martensson B, Scalia, Tomba GP, Thoren P (1984). CSF monoamine metabolites in melancholia. *Acta Psychiatrica Scandinavica 69*, 201–219.

Avissar S, Nechamkin Y, Roitman G, Schreiber G (1997). Reduced G protein functions and immunoreactive levels in mononuclear leukocytes of patients with depression. *American Journal of Psychiatry 154*, 211–217.

Ball WA, Whybrow PC (1993). Biology of depression and mania. *Current Opinion in Psychiatry 6*, 27–34.

Baumann B, Danos P, Diekmann S, Bielau H, Gerecke N, Bernstein HG, Bogerts B (1998). Postmortem analysis of noradrenergic and serotonergic brainstem systems in mood disorders. *European Archives of Psychiatry and Clinical Neuroscience 248* (Suppl. 2), S79.

Baumann B, Danos P, Krell D, Diekmann S, Wurthmann C, Bielau H, et al. (1999). Unipolar-bipolar dichotomy of mood disorders is supported by noradrenergic brainstem system morphology. *Journal of Affective Disorders 54*, 217–224.

Baxter Jr. LR, Phelps ME, Mazziotta JC, Schwartz JM, Gerner RH, Selin CE, Sumida RM (1985). Cerebral metabolic rates for glucose in mood disorders. Studies with positron emission tomography and fluorodeoxyglucose F18. *Archives of General Psychiatry 42*, 441–447.

Baxter Jr. LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry 46*, 243–250.

Becker G, Becker T, Berg D, Hofmann E, Lange K, Struck M (1998a). Pathological findings in neuropsychiatric disorders. In: Bogdahn U, Becker G, Schlachetzki F (Eds.), *Echoenhancers and Transcranial Color Duplex Sonography* (pp. 395–368). Berlin, Vienna: Blackwell.

Becker G, Becker T, Struck M, Lindner A, Burzer K, Retz W, et al. (1995a). Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. *Biological Psychiatry 38*, 180–184.

Becker G, Berg D, Rausch WD, Lange KW, Riederer P, Reiners K (1999). Increased tissue copper and manganese content of the lentiform nucleus in primary adult-onset dystonia. *Annals of Neurology 46*, 260–263.

Becker G, Griewing B (1998). Examination techniques. In: Bogdahn U, Becker G, Schlachetzki F (Eds.), *Echoenhancers and Transcranial Color Duplex Sonography* (pp. 219–231). Berlin, Vienna: Blackwell.

Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K (1995b). Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. *Neurology 45*, 182–184.

Becker G, Struck U, Bogdahn U, Becker T (1994). Echogenicity of the brainstem raphe in patients with major depression. *Psychiatry Research 55*, 75–84.

Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, et al. (1997). Parkinson's disease and depression, evidence for an alteration of the basal limbic system detected by transcranial sonography. *Journal of Neurology, Neurosurgery and Psychiatry 63*, 590–596.

Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ (1992). The anatomy of melancholia-focal abnormalities of cerebral blood flow in major depression. *Psychological Medicine 22*, 607–615.

Bench CJ, Frackowiak RS, Dolan RJ (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychological Medicine 25*, 247–261.

Berg D, Becker G, Zeiler B, Tucha O, Hofmann E, Preier M, et al. (1999a). Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. *Neurology 53*, 1026–1031.

Berg D, Supprian T, Hofmann E, Zeiler B, Jäger A, Lange KW, et al. (1999b). Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. *Journal of Neurology 246*, 1186–1193.

Berg D, Supprian T, Thomae J, Warmuth-Metz M, Horowski A, Zeiler B, et al. (2000). Multiple sclerosis and depression – pathogenetic differences compared with depression in neurodegenerative disorders. *Multiple Sclerosis 6*, 156–162.

Biver F, Wikler D, Lotstra F, Damhaut P, Goldman S, Mendlewicz J (1997). Serotonin 5-HT2 receptor imaging in major depression: focal changes in orbito-insular cortex. *British Journal of Psychiatry 171*, 444–448.

Bogdahn U, Becker G, Winkler J, Greiner K, Perez J, Meurers B (1990). Transcranial color-coded real-time sonography in adults. *Stroke 21*, 1680–1688.

Brücke T, Sofic E, Riederer P, Gabriel E, Jellinger K, Danielczyk W (1984). Die Bedeutung der serotonergen Raphe-Kortex-Projektion für die Beeinflussung der adrenergen Neurotransmission durch Antidepressiva. *Neuropsychiatria Clinica 3*, 249–255.

Buchsbaum MS, Wu J, DeLisi LE, Holcomb H, Kessler R, Johnson J, et al. (1986). Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography

with [^{18}F]2-deoxyglucose in affective illness. *Journal of Affective Disorders 10*, 137–152.

Chan-Palay V, Asan E (1989). Quantification of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. *Journal of Comparative Neurology 287*, 357–372.

Carpenter MB, Sutin J (1993). *Human Neuroantomy* (pp. 403–453, 560–567, 639–642). Baltimore: Williams and Wilkins.

Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC, et al. (1993). Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. *Archives of General Psychiatry 50*, 7–16.

Collier DA, Stöber G, Li T, Heils A, Catalano M, Di Bella D, et al. (1996). A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Molecular Psychiatry 1*, 453–460.

Craddock N, Jones I (1999). Genetics of bipolar disorder. *Journal of Medical Genetics 36*, 585–594.

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. (1999). PET imaging of serotonin 1A receptor binding in depression. *Biological Psychiatry 46*, 1375–1387.

Duman RS, Heninger GR, Nestler EJ (1997). A molecular and cellular theory of depression. *Archives of General Psychiatry 54*, 597–606.

Ebert D, Feistel H, Barocka A (1991). Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99m-HMPAO SPECT. *Psychiatry Research 40*, 247–251.

Fibiger HC (1984). The neurobiological substrates of depression in Parkinson's disease. *Canadian Journal of Neurological Sciences 11*, 105–107.

Garcia-Sevilla JA, Escriba PV, Ozaita A, La Harpe R, Walzer C, Eytan A, Guimon J (1999). Up-regulation of immunolabeled alpha2A-adrenoceptors, Gi coupling proteins, and regulatory receptor kinases in the prefrontal cortex of depressed suicides. *Journal of Neurochemistry 72*, 282–291.

Geyer MA, Puerto A, Dawsey WJ, Knapp S, Bullard WP, Mandell AJ (1976). Histological and enzymatic studies of the mesolimbic and mesostriatal serotonergic pathways. *Brain Research 106*, 241–256.

Glowinski J, Tassin JP, Thierry AM (1984). The meso-cortico-prefrontal dopaminergic neurons. *Trends in Neuroscience 7*, 415–418.

Goodwin FK, Post RM, Dunner DL, Gordon EK (1973). Cerebrospinal fluid amine metabolites in affective illness. The probenecid technique. *American Journal of Psychiatry 130*, 73–79.

Gutierrez B, Pintor L, Gasto C, Rosa A, Bertranpetit J, Vieta E, Fananas L (1998). Variability in the serotonin transporter gene and increased risk for major depression with melancholia. *Human Genetics 103*, 319–322.

Hillegaart V (1991). Functional topography of brain serotonergic pathways in rat. *Acta Physiologica Scandinavica* (Suppl.) *598*, 1–54.

Holstege G (1990). Subcortical limbic system projections to the caudal brainstem and spinal cord. In: Paxinos G (Ed.), *The Human Nervous System* (pp. 261–286). San Diego, New York, Boston: Academic Press.

Husain MM, McDonald WM, Doraiswamy PM, Figiel GS, Na C, Escalona PR, et al. (1991). A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Research 40*, 95–99.

Inglis WL, Winn P (1995). The pedunculopontine tegmental nucleus, where the striatum meets the reticular formation. *Progress in Neurobiology 47*, 1–29.

Ito H, Kawashima R, Awata S, Ono S, Sato K, Goto R, et al. (1996). Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *Journal of Nuclear Medicine 37*, 410–414.

Jeste DV, Lohr JB, Goodwin FK (1988). Neuroanatomical studies of major affective disorders. A review and suggestions for further research. *British Journal of Psychiatry 153*, 444–459.

Jones B (1991). The role of noradrenergic locus coeruleus neurons and neighboring cholinergic neurons of the pontomesencephalic tegmentum in sleep-wake states. *Progress in Brain Research 88*, 533–543.

Jones SL (1991). Descending noradrenergic influences on pain. *Progress in Brain Research 88*, 381–394.

Joyce PR, Paykel ES (1989). Predictors of drug response in depression. *Archives of General Psychiatry 46*, 89–99.

Kendler KS, Gardner CO, Prescott CA (1999). Clinical characteristics of major depression that predict risk of depression in relatives. *Archives of General Psychiatry 56*, 322–327.

Kienzl E, Eichinger K, Sofic E, Jellinger K, Riederer P, Kuhn W, et al. (1990). Urinary dopamine sulfate: regulations and significance in neurological disorders. *Journal of Neural Transmission* (Suppl.) *32*, 471–479.

Kitayama I, Yaga T, Kayahara T, Nakano K, Murase S, Otani M, Nomura J (1997). Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. *Biological Psychiatry 42*, 687–696.

Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA (1997). Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. *Journal of Neuroscience 17*, 8451–8458.

Kostic VS, Dijuric BM, Covickovic-Sternic N, Bumbasirevic L, Nicolic M, Mrsulja BB (1987). Depression and Parkinson's disease: possible role of serotonergic mechanisms. *Journal of Neurology 234*, 94–96.

Krishnan KR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, et al. (1992). Magnetic resonance imaging of the caudate nuclei in depression. Preliminary observations. *Archives of General Psychiatry 49*, 553–557.

Lang J (1993). Surgical anatomy of the brainstem. *Neurosurgery Clinics of North America 3*, 367–403.

Larisch R, Klimke A, Vosberg H, Loffler S, Gaebel W, Muller-Gartner HW (1997). In vivo evidence for the involvement of dopamine-D2 receptors in striatum and anterior

cingulate gyrus in major depression. *Neuroimage 5*, 251–260.

Leonard BE (1997). The role of noradrenalin in depression: a review. *Journal of Psychopharmacology 11*, S39–S47.

Lesch KP, Mössner R (1998). Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders. *Biological Psychiatry 44*, 179–192.

Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, et al. (1998). Reduced brain serotonin transporter availability in major depression as measured by [^{123}I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biological Psychiatry 44*, 1090–1098.

Manki H, Kanba S, Muramatsu T, Higuchi S, Suzuki E, Matsushita S, et al. (1996). Dopamine D2, D3 and D4 receptor and transporter gene polymorphisms and mood disorders. *Journal of Affective Disorders 40*, 7–13.

Mann JJ (1999). Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology 21*(Suppl.), 99S–105S.

Martinot JL, Hardy P, Feline A, Huret JD, Mazoyer B, Attar-Levy D, et al. (1990). Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *American Journal of Psychiatry 147*, 1313–1317.

Mayberg HS, Lewis PJ, Regenold W, Wagner Jr. HN (1994). Paralimbic hypoperfusion in unipolar depression. *Journal of Nuclear Medicine 35*, 929–934.

Mayberg HS, Starkstein SE, Sadzot B, Preziosi T, Andrezejewski PL, Dannals RF, et al. (1990). Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Annals of Neurology 28*, 57–64.

Mayeux R, Stern Y, Sano M, Williams JB, Cote C (1988). The relationship of serotonin to depression in Parkinson's disease. *Movement Disorders 3*, 237–244.

Mayeux R, Stern Y, Williams JBW, Coten L, Frantz A, Dryenfurth I (1986). Clinical and biochemical features of depression in Parkinson's diesase. *American Journal of Psychiatry 143*, 756–759.

Menza MA, Palermo B, DiPaola R, Sage JI, Ricketts MH (1999). Depression and anxiety in Parkinson's disease: possible effect of genetic variation in the serotonin transporter. *Journal of Geriatric Psychiatry and Neurology 12*, 49–52.

Molchan SE, Lawlor BA, Hill JL, Martinez RA, Davis CL, Mellow AM, et al. (1991). CSF monoamine metabolites and somatostatin in Alzheimer's disease and major depression. *Biological Psychiatry 29*, 1110–1118.

Moore CM, Christensen JD, Lafer B, Fava M, Renshaw PF (1997). Lower levels of nucleoside triphosphate in the basal ganglia of depressed subjects: a phosphorous-31 magnetic resonance spectroscopy study. *American Journal of Psychiatry 154*, 116–118.

Mössner R, Schmitt A, Syagailo Y, Gerlach M, Riederer P, Lesch KP (In Press). The serotonin transporter in Alzheimer's and Parkinson's disease. *Journal of Neural Transmission*.

Naumann M, Becker G, Toyka KV, Supprian T, Reiners K (1996). Lenticular nucleus lesion in idiopathic dystonia detected by transcranial sonography. *Neurology 47*, 1284–1290.

Niewenhuys R (1985). *Chemoarchitecture of the Brain* (pp. 144–158). Berlin: Springer Verlag.

Ogilvie AD, Battersby S, Bubb VJ, Fink G, Harmar AJ, Goodwim GM, Smith CA (1996). Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet 347*, 731–733.

Oruc L, Verheyen GR, Furac I, Ivezic S, Jakovljevic M, Raeymaekers P, Van Broeckhoven C (1997). Positive association between the GABRA5 gene and unipolar recurrent major depression. *Neuropsychobiology 36*, 62–64.

Papeschi R, McClure DJ (1971). Homovanillic and 5-hydroxyindoleacetic acid in cerebrospinal fluid of depressed patients. *Archives of General Psychiatry 25*, 354–335.

Paulus W, Jellinger K (1991). The neuropathologic basis of different clinical subgroups of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology 50*, 743–755.

Pratt JA (1992). The neuroanatomical basis of anxiety. *Pharmacology and Therapeutics 55*, 149–181.

Puls I, Berg D, Hetzel G, Schließer M, Becker G (2000). Comparison of B-mode imaging and tissue harmonic imaging. *Ultrasound in Medicine and Biology 26*, 189–194.

Renshaw PF, Lafer B, Babb SM, Fava M, Stoll AL, Christensen JD, et al. (1997). Basal ganglia choline levels in depression and response to fluoxetine treatment: an in vivo proton magnetic resonance spectroscopy study. *Biological Psychiatry 41*, 837–843.

Ring HA, Bench CJ, Trimble MR, Brooks DJ, Frackowiak RS, Dolan RJ (1994). Depression in Parkinson's disease. A positron emission study. *British Journal of Psychiatry 165*, 333–339.

Roy A, Pickar D, Linnoila M, Doran AR, Ninan P, Paul SM (1985). Cerebrospinal fluid monoamine and monoamine metabolite concentrations in melancholia. *Psychiatry Research 15*, 281–292.

Rubin E, Sackeim HA, Prohovnik I, Moeller JR, Schnur DB, Mukherjee S (1995). Regional cerebral blood flow in mood disorders. IV. Comparison of mania and depression. *Psychiatry Research 61*, 1–10.

Sano M, Stern Y, Williams J, Cote L, Rosenstein R, Mayeux R (1989). Coexisting dementia and depression in Parkinson's disease. *Archives of Neurology 46*, 1284–1286.

Sastre M, Garcia-Sevilla JA (1997). Densities of I2-imidazoline receptors, alpha 2-adrenoceptors and monoamine oxidase B in brains of suicide victims. *Neurochemistry International 30*, 63–72.

Sawynok J, Reid AR, Doak GJ (1995). Caffeine antinociception in the rat hot-plate and formalin tests and locomotor stimulation: involvement of noradrenergic mechanisms. *Pain 61*, 203–213.

Schildkraut JJ (1973). Neuropharmacology of affective

disorders. *Annual Review of Psychopharmacology 13*, 427–454.

Shah SA, Doraiswamy PM, Husain MM, Escalona PR, Na C, Figiel GS, et al. (1992). Posterior fossa abnormalities in major depression: a controlled magnetic resonance imaging study. *Acta Psychiatrica Scandinavica 85*, 474–479.

Shelton RC, Mainer DH, Sulser F (1996). cAMP-dependent protein kinase activity in major depression. *American Journal of Psychiatry 153*, 1037–1042.

Simpson PE, Weiss JM (1988). Altered activity of the locus coeruleus in animal models of depression. *Neuropsychopharmacology 1*, 287–295.

Staley JK, Malison RT, Innis RB (1998). Imaging of the serotonergic system: interactions of neuroanatomical and functional abnormalities of depression. *Biological Psychiatry 44*, 534–549.

Stevens JR, Livermore Jr. A (1978). Kindling of the mesolimbic dopamine system: animal model of psychosis. *Neurology 28*, 36–46.

Syvalahti E (1987). Monoaminergic mechanisms in affective disorders. *Medical Biology 65*, 89–96.

Torack RM, Morris JC (1988). Association of ventral tegmental area histopathology with adult dementia. *Archives of Neurology 45*, 497–501.

van Praag HM, Korf J (1975). Central monoamine deficiency in depressions, causative or secondary phenomenon? *Pharmakopsychiatrie – Neuro-Psychopharmakologie 8*, 322–326.

van Praag HM, Korf J, Schut D (1973). Cerebral monoamines and depression. An investigation with the probenecid technique. *Archives of General Psychiatry 28*, 827–831.

Weiss JM, Stout JC, Aaron MF, Quan N, Owens MJ, Butler PD, Nemeroff C (1994). Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Research Bulletin 35*, 561–572.

Willick ML, Kokkinidis L (1995). The effects of ventral tegmental administration of GABAA, GABAB and NMDA receptor agonists on medial forebrain bundle self-stimulation. *Behavioral Brain Research 70*, 31–36.

Yatham LN, Liddle PF, Dennie J, Shiah IS, Adam MJ, Lane CJ, et al. (1999). Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment, a positron emission tomography study with fluorine-18-labeled setoperone. *Archives of General Psychiatry 56*, 705–711.

Yavari P, Vogel GW, Neill DB (1993). Decreased raphe unit activity in a rat model of endogenous depression. *Brain Research 611*, 31–36.