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

Georg Becker¹, Daniela Berg¹, Klaus Peter Lesch³ and Thomas Becker²

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.

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; Papieschi 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., 1990). 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.
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 structures. 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.](image-url)
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 (★).

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 sagitally 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 pathophysiological 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., 1997). 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)

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

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