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Evaluation of basal ganglia, brainstem raphe and ventricles in bipolar disorder by transcranial sonography

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ABSTRACT

Transcranial brain sonography (TCS) has become a reliable and sensitive diagnostic tool in the evaluation of extrapyramidal movement disorders. Alterations of brainstem raphe (BR) have been depicted by TCS in major depression but not in bipolar disorder. The aim of our study was to evaluate BR echogenicity depending on the different conditions of bipolar patients. Echogenicities of dopaminergic basal ganglia structures were assessed for the first time in bipolar disorder. Thirty-six patients with bipolar I disorder (14 depressed, 8 manic, 14 euthymic) were compared to 35 healthy controls. Echogenicities were investigated according to the examination protocol for extrapyramidal disorders using a Siemens Sonoline® Elegra system. The sonography examiner was blinded for clinical rating scores. Six patients (16.7%) showed hyperechogenicity of the substantia nigra. The raphe was hypoechogenic in 13 (36.1%) of the patients. No significant differences were seen between the subgroups. Compared to the control group, frequency of altered echogenicities did not reach statistical significance. The width of third ventricle was significantly larger in the patient group (3.8± −2.1 mm vs. 2.7±1.2 mm). Depressed bipolar patients with reduced BR echogenicity showed significantly higher scores on the Hamilton Depression Rating Scale as well as the Montgomery-Åsberg Depression Rating Scale. In contrast to unipolar depression, sonographic findings of bipolar patients may generally indicate structural integrity of mesencephalic raphe structures. If bipolar disorder coexists with hypoechogenic raphe structure, depressive symptoms are more severe.

1. Introduction

Transcranial sonography (TCS) depicts the echogenicity (intensity of reflected ultrasound waves) in different parenchymal regions of the brain. TCS has become a reliable and sensitive diagnostic tool in the evaluation of extrapyramidal movement disorders, especially in the differentiation of parkinsonian syndromes (Walter et al., 2003; Berg et al., 2008). Hyperechogenicity of the substantia nigra is a highly characteristic finding for idiopathic Parkinson's disease (Becker et al., 1995b; Walter et al., 2003; Berg et al., 2008). It is assumed that this echo signal alteration is based on increased amounts of iron, bound to proteins other than ferritin (Berg et al., 2002). Furthermore, alterations of brainstem raphe (BR) have been observed by TCS in major depression and in depressed patients with Parkinson's disease (Becker et al., 1995a, 2001; Berg et al., 1999; Walter et al., 2007b, c).

Bipolar affective disorders are characterized by recurrent episodes of depression as well as mania or hypomania (American Psychiatric Association, 2000). In histological studies, subtle structural deficits in the dorsal raphe with a regional reduction in the synthesis of noradrenalin have been described in patients with bipolar disorder (Baumann and Bogerts, 2001). The mesencephalic brainstem region is one of the few regions that can be investigated well by means of TCS (Berg et al., 2008).

Up to now, there is only one TCS study evaluating BR alterations in patients with bipolar affective disorders, revealing normal or even increased echogenicity of BR, irrespective of the existing disease conditions (Becker et al., 1995a). This observation led to the assumption that reduced echogenicity of BR may be specific to unipolar depression (Becker et al., 1995a).

The aim of our study was to evaluate BR echogenicity depending on the different conditions of bipolar I disorder patients. We hypothesized that hypoechogenic BR would be detected more frequently in

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the depressive subgroup compared to the other patient subgroups. Thus, frequency of hypoechogenic brainstem raphe in patients with bipolar disorder with current depressive episode is compared to findings in patients with bipolar disorder in remission, as well as with current manic episode. In addition, the echogenicity of the substantia nigra (SN) was assessed for the first time in bipolar affective disorder. This is of particular interest since additional SN alterations have been described recently as a frequent finding in patients with depressive symptoms (Walter et al., 2007b). Thus, a second hypothesis was that alterations of dopaminergic basal ganglia would be detected more frequently in the patient group than in the control group. Furthermore, recent studies postulate a dopaminergic dysfunction in the pathophysiology of bipolar affective disorders (Berk et al., 2007).

In the present study, a complete sonographic evaluation, determining echogenicities of serotonergic brainstem raphe nuclei as well as of dopaminergic basal ganglia, is performed for the first time in this disease entity.

2. Methods

2.1. Subjects

The sample consisted of 40 inpatients or outpatients with unequivocal diagnosis of bipolar I disorder. Patients were consecutively recruited from the Department of Psychiatry of the Ruhr University Bochum. Initially, we aimed to have 15 patients in each group of bipolar depression, mania and euthymia. Group membership determined using the Mini-International Neuropsychiatric Interview for DSM-IV (American Psychiatric Association, 2000) diagnosis of a current manic, depressed or remitted episode.

Four patients (9.7%) were excluded due to an inadequate temporal bone window for ultrasound examination. Further exclusion criteria were organic psychiatric disorders or recent concomitant neurological disorders (5 patients). Table 1 shows the demographic and clinical data of 36 bipolar I disorder patients who were included in the study. All patients received optimal medical treatment including antidepressant or antimanic medication or mood stabilizers (Table 2).

Initially, a control group of 15 healthy volunteers was created. These 15 persons underwent specific tests for depressive symptoms (HAM-D, MADRS and BDI) as well as for manic syndromes (see Section 2.2). To improve statistical analysis, the control group was expanded with 20 further healthy persons from a pre-existing group of healthy persons who form the reference group of our sonography laboratory.

Thus, 35 healthy volunteers without any neurological or psychiatric disorders in personal or family history served as an age-matched control group. They were recruited from the hospital staff, the medical student body as well as from the circle of their friends and family. Their demographic data are also shown in Table 1. All subjects gave written informed consent after the study was fully explained to them.

In accordance to the Helsinki Declaration of 1975, the study was approved by the local university ethics committee of the Ruhr University Bochum, Germany.

2.2. Clinical assessment

Clinical interviews and ratings were performed by a consultant in psychiatry or by a trained and experienced interviewer. Diagnosis of bipolar I disorder was confirmed using the structured Mini-International Neuropsychiatric Interview (MINI) for DSM-IV diagnosis (Sheehan et al., 1998). We excluded patients with diagnosis of mixed episode or rapid cycling. In addition, we collected data about previous episodes, the number and symptoms of episodes, age of onset of psychiatric disorder, age of first diagnosis of bipolar disorder, hospitalization rate and comorbidity. Moreover, pharmacological treatment and other therapeutic intervention were recorded.

Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Scale (MADRS) and self-ratings with Beck's Depression Inventory (BDI) (Beck et al., 1961; Hamilton, 1967; Montgomery and Åsberg, 1979). Severity of manic symptoms was evaluated using the Young Mania Rating (YMRS) and the Self-Report Manic Inventory (SRMI) (Young et al., 1978; Krüger et al., 1997). Severity of symptoms was defined on the YMRS with cutoff scores of >=16 for mild mania and on the HAM-D with >=16 points for mild depression. Euthymia was not explicitly defined by any symptom cutoffs. The overall severity of the psychiatric disorder was quantified using the Clinical Global Impression score (CGI) and Global Assessment of Functioning Scale (GAF).

In the control group, scores on the HAM-D and the BDI were obtained in all 35 healthy volunteers. Specific tests for manic

Table 1
Demographic and clinical variables of bipolar I disorder patients and healthy controls.

Variables	Bipolar depressive		Bipolar manic		Bipolar euthymic		Healthy controls		*H*	*d.f.*	*P*
	(*n* = 14)		(*n* = 8)		(*n* = 14)		(*n* = 35)				
	Mean (S.D.)		Mean (S.D.)		Mean (S.D.)		Mean (S.D.)				
Age [y]	40.4 (14.2)		48.1 (17.6)		44.9 (11.2)		37.4 (11.2)		5.44	3	0.14
Age at onset of psychiatric disease [y]	29.4 (7.9)		22.1 (11.5)		31.4 (9.7)		–		4.58	2	0.10
Age [y] at diagnosis of bipolar disorder	35.4 (10.3)		31.1 (16.3)		35.5 (9.0)		–		0.86	2	0.65
Hospitalizations [n]	6.9 (7.5)		6.5 (2.5)		4.9 (4.0)		–		2.12	2	0.35
Manic episodes [n]	7.6 (9.1)		8.0 (6.2)		10.9 (7.0)		–		2.29	2	0.32
Depressive episodes [n]	17.5 (26.5)		15.6 (12.7)		14.6 (16.5)		–		0.43	2	0.81
Total episodes [n]	24.1 (34.9)		23.6 (13.9)		25.4 (22.1)		–		1.34	2	0.51
BDI	37.2 (12.5)		14.1 (6.0)		10.1 (8.6)		3.8 (4.1)		19.74	3	<0.01
SRMI	13.3 (8.6)		17.6 (11.4)		8.4 (8.3)		1.7[a] (2.9)[a]		19.57	3	<0.01
HAM-D	21.8 (3.8)		10.1 (4.2)		7.6 (5.7)		1.9 (1.7)		38.25	3	<0.01
MADRS	29.2 (6.7)		8.5 (5.4)		8.4 (6.1)		1.5[a] (1.8)[a]		37.29	3	<0.01
YMRS	3.9 (3.9)		22.8 (4.8)		6.7 (5.3)		0.4[a] (0.7)[a]		31.13	3	<0.01
GAF	49.3 (9.4)		40.0 (14.1)		68.6 (15.0)		85.0[a] (0.0)[a]		36.74	3	<0.01
CGI	4.7 (0.7)		5.3 (1.3)		2.4 (1.3)		1.0[a] (0.0)[a]		38.8	3	<0.01
	N	%	*N*	%	*n*	%	*N*	%	χ^2	*d.f*	*P*
Sex (f/m)	7/7	50/50	3/5	38/63	6/8	43/57	19/16	54/46	1.01	3	0.80

H = Kruskal–Wallis-test; *d.f.* = degrees of freedom; BDI = Beck-Depression-Inventory; MSS = Mania-Self-Rating Scale; HAMD = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale; SRMI = Self-Report Manic Inventory; GAF = Global Assessment of Functioning Scale; CGI = Clinical Global Impression Scale.

[a] Performed only in 15 of the 35 controls.

Table 2
Psychopharmacological medication and daily dose.

	n	Daily dose, mg
		Median (range)
Valproic acid	13	800 (500–1500)
Lithium carbonate	10	986 (450–1608)
Olanzapine	9	10 (5–15)
Aripiprazole	5	15 (10–30)
Escitalopram	3	15 (10–15)
Venlafaxine	3	150 (15–225)
Lorazepam	3	1 (1–1)
Amisulpride	3	400 (400–400)
Promethazine	2	25 (25–25)
Carbamazepine	2	550 (500–600)
n = 1: Bupropion 300/d	Chlorprothixene 50/d	Citalopram 20/d
Diazepam 10/d	Duloxetine 60/d	Flupentixol 1/d
Levomepromazine 150/d	Mirtazapine 45/d	Moclobemide 300/d
Reboxetine 12/d	Sertaline 50/d	Trazodone 100/d
Trimipramine 50/d	Zuclopenthixol 150/d	

syndromes (YMRS and SRMI) as well as the MADRS were performed in 15 controls.

2.3. Transcranial sonography

Each of the subjects had sonographic as well as psychiatric examinations at the same day. TCS was performed by a single experienced investigator blinded to the clinical scores (C.K.) using a phased array ultrasound system equipped with a 2.5-MHz transducer (Sonoline Elegra System, Siemens, Erlangen, Germany). Patients were not allowed to talk with the examiner about their psychiatric symptoms. A penetration depth of 150 mm and a dynamic range of 45 dB were chosen. Image brightness and time gain compensations were adapted as needed for each examination. The examination protocol was based on previous published recommendations for TCS (Walter et al., 2007a): Using the transtemporal approach, the midbrain and diencephalic examination planes were visualized in axial section. In case of hyperechogenicity of SN, a planimetric measurement was performed. Sizes of less than 0.20 cm^2 were defined as normal, sizes between 0.20 and 0.25 cm^2 were classified as moderately and sizes of 0.25 cm^2 and above were graded as markedly hyperechogenic. Echogenicity of BR was classified semi-quantitatively on a three point scale using the red nucleus as a reference point: 0 = raphe structure not visible, 1 = slight and interrupted echogenic raphe structure, 2 = normal echogenicity (echogenicity of raphe structure is not interrupted and intensity is equal to that of the red nucleus). Echogenicities of the thalami, lentiform nucleus (LN) and the head of the caudate nucleus (CN) were examined and graded as hyperechogenic if they were more intense than the surrounding white matter. The maximal width of the frontal horns of the side ventricles and in parallel line the distance between the septum pellucidum and the head of CN as well as the minimal transverse diameter of the third ventricle were measured on a standardized diencephalic examination plane. The minimal transverse diameter of the third ventricle was measured on a standardized diencephalic examination plane. The sonographic findings were printed and stored, so that a second experienced TCS investigator (J.E.), who was also blinded to the clinical ratings, performed a second independent evaluation and classification of the results. In the case of discrepant ratings a consensus was accomplished, subsequently.

2.4. Statistical analysis

Descriptive statistics are given as mean values and standard deviation (S.D.) consistently throughout the manuscript. As needed, the range is given additionally. Inter-rater agreement was analysed by Cohen's kappa statistics and the agreement was estimated according to a classification proposed by Landis and Koch (1977). Statistical comparison of groups and correlation analysis were performed by appropriate nonparametric tests (Kruskal-Wallis H test, Mann-Whitney–*U* test, Fisher's exact test also with Freeman–Halton extension in case of two rows by three columns contingency table with SPSS 17.0 for Windows.

3. Results

3.1. Clinical features

Fourteen (38.9%) of the patients fulfilled the diagnostic criteria for depressive episode (age = 40.4 ± 14.2y; HAM-D = 21.8 ± 3.8; MADRS = 29.2 ± 6.7; BDI = 37.2 ± 12.5). In eight (22.2%) of the patients a manic episode could be diagnosed (age = 48.4 ± 17.6y; YMRS = 22.8 ± 4.8; SRMI = 12.3 ± 8.6). Fourteen (38.9%) of the bipolar patients were classified as remitted bipolar disorder (age = 44.9 ± 11.22y; HAM−D = 7.6 ± 5.7; MADRS = 8.4 ± 6.1; BDI = 10.1 ± 8.6; YMRS = 6.7 ± 5.3; SRMI = 8.4 ± 8.3).

Between the three groups there was neither a significant difference in the number of previous depressive or manic episodes nor in the number of earlier hospitalizations.

Detailed demographic and clinical data of the bipolar I patients as well as of the control group are given in Table 1.

3.2. Transcranial brain sonography findings

Due to partially insufficient bone window in 10 (27.8%) of the 36 patients, an adequate evaluation of the lateral ventricles could not be performed bilaterally, so that only the width of the third ventricle was used for further statistical analysis. In two (5.6%) of the patients, the anterior part of the bone window was bilaterally insufficient, so that CN and LN could not be evaluated sufficiently. Evaluation of width of third ventricle, SN and BR could be performed in all 36 patients with bipolar disorder.

The mean width of the third ventricle was 3.8 ± 2.1 mm (range = 1.3–10.1 mm). Six (16.7%) patients showed SN-hyperechogenicities (4 unilateral, 2 bilateral, see Table 3). Four of them exhibited marked hyperechogenicity, two of them bilaterally. The median area of SN echogenic size of all patients with bipolar disorder was 0.08 ± 0.11 cm^2 (range = 0.00–0.33 cm^2). Three (8.8%) of 34 patients exhibited hyperechogenicity of CN (all unilaterally). Four (11.8%) of 34 patients showed hyperechogenicities of LN (two bilaterally). In one patient hyperechogenicities were detected in two different regions (CN+LN). Thirteen (36.1%) of 36 patients showed conspicuous signal of BR. In 10 of the BR echogenicity was reduced (Grade 1), while in three patients BR was not visible (Grade 0, see Fig. 1).

The two sonographers agreed independently in 30 (83.3%) of the 36 BR-gradings, resulting in a good agreement (Cohen's weighted kappa = 0.748). There was unambiguous consent in the classifications of SN, LN and CN findings.

3.3. Comparison of TCS findings between bipolar patients and healthy controls

In patients with bipolar disorder, the width of the third ventricle was slightly but significantly larger in comparison to that of healthy controls (3.8 ± 2.1 mm and 2.7 ± 1.2 mm respectively; *U*-Test, $p = 0.025$). Three (8.6%), two (5.7%) and three (8.6%) controls had hyperechogenic lesions of SN, CN and LN, respectively. Seven (20.0%) of the 35 controls exhibited reduced BR echogenicity, but in one case (2.9%) BR was not visible. Statistically, there was no significant difference in the presentation of pathologic BR signal between the two groups (Fisher's exact test, $p = 0.187$). The detected echogenicities of both groups are summarized in Table 3.

Table 3
Evaluation of brain parenchyma echogenicities in patients with bipolar disorder in comparison to healthy controls.

Structure	Bipolar patients, $n=36$		Healthy controls, $n=35$		Significance
Width of third ventricle, mm					$p=0.025$[a]
	3.8 ± 2.1		2.7 ± 1.2		$U=448.5$
	(1.3–10.1)		(0.8–6.3)		$Z=2.23$
					$d.f.=1$
Substantia nigra (SN)	Normal: 30 (83.3%)	Hyperechogenic: 6 (16.7%) Moderate: 2; marked: 4 UL: 2 BL: 0; UL: 2 BL: 2	Normal: 32 (91.4%)	Hyperechogenic: 3 (8.6%) Moderate: 2; marked: 1 UL: 2 BL: 0; UL: 0 BL: 1	$p=0.478$[b] (n.s.) $d.f.=1$
Caudate nucleus	Normal: 31 (91.2%)[c]	Hyperechogenic: 3 (8.8%)[c] UL: 3 BL: 0	Normal: 33 (94.3%)	Hyperechogenic: 2 (5.7%) UL: 1 BL: 1	$p=0.673$[b] (n.s.) $d.f.=1$
Lentiform nucleus	Normal: 30 (88.2%)[c]	Hyperechogenic: 4 (11.8%)[c] UL: 2 BL: 2	Normal: 32 (91.4%)	Hyperechogenic: 3 (8.6%) UL: 3 BL: 0	$p=0.709$[b] (n.s.) $d.f.=1$
Mesencephalic raphe	Normal: 23 (63.9%)	Hypoechogenic: 13 (36.1%) Reduced: 10; not visible: 3	Normal: 28 (80.0%)	Hypoechogenic: 7 (20.0%) Reduced: 6; not visible: 1	$p=0.187$[b] (n.s.) $d.f.=1$

UL = unilateral; BL: bilateral.
[a] Mann–Whitney *U* test.
[b] Fisher's exact test (n.s. = not significant).
[c] Evaluation performed only in 34 of the bipolar patients.

3.4. Comparison of TCS findings between subgroups of bipolar patients

Hypoechogenicity of BR was depicted in six (42.9%) of the depressed, in three (37.5%) of the manic and in four (28.6%) of the euthymic bipolar patients. Thus, no significant difference was seen between the three subgroups (Freeman–Halton test, $p=0.684$). The particular intra-subgroup analysis of BR echogenicities revealed that within the bipolar depressive group, conspicuous findings of BR correlated significantly with the severity of depressive symptoms estimated by the scores of HAM-D and MADRS (*U*-Test, $U=40.5$, $Z=-2.07$, $p=0.029$ and *U*-Test, $U=42$, $Z=-2.26$, $p=0.020$ respectively, see Fig. 2). No correlation was seen between the severity of manic symptoms estimated by the scores of MSS and YMRS (*U*-Test, $U=145.5$, $Z=0.12$, $p=0.678$ and *U*-Test, $U=144$, $Z=0.16$, $p=0.654$ respectively). No correlation was seen between BR hypoechogenicity and number of depressive or manic episodes in history (*U*-Test, $U=170.5$, $Z=-0.68$, $p=0.372$ and *U*-Test, $U=165.5$, $Z=-0.51$, $p=0.457$ respectively). Also, no relationship between BR hypoechogenicity and hospitalizations was seen (*U*-Test, $U=202$, $Z=-1.71$, $p=0.132$).

Relating to echogenicity of SN, a strong trend of more frequent SN hyperechogenicities in the depressed subgroup was identified (Freeman–Halton test, $p=0.069$). Hyperechogenic SN was seen in five (35.7%) of the depressed, in none (0%) of the manic and in one (7.1%) of the euthymic patients (see Table 4).

No significant relationship between substantia nigra hyperechogenicity and number of depressive or manic episodes in history was seen (*U*-Test, $U=119.5$, $Z=-1.23$, $p=0.164$ and *U*-Test, $U=96$, $Z=-0.23$, $p=0.614$ respectively). Also, no relationship between SN hyperechogenicity and hospitalizations was seen (*U*-Test, $U=98.5$, $Z=-0.34$, $p=0.550$).

No differences were found in the frequencies of the hyperechogenicities of CN and LN between the three subgroups (Freeman–Halton test, $p=0.781$ and $p=0.420$ respectively).

4. Discussion

One of the main conclusions to be drawn from the study is that sonographic findings do not differ in different mood states of bipolar I disorder. Regarding the brainstem raphe, hypoechogenicity is correlated to the severity of symptoms in bipolar depression. Furthermore, bipolar patients in general showed significantly larger widths of the third ventricle than the control group in our study.

SN hyperechogenicity is a frequent observation in patients with Parkinson's disease (Becker et al., 1995b; Berg et al., 2008). It is assumed

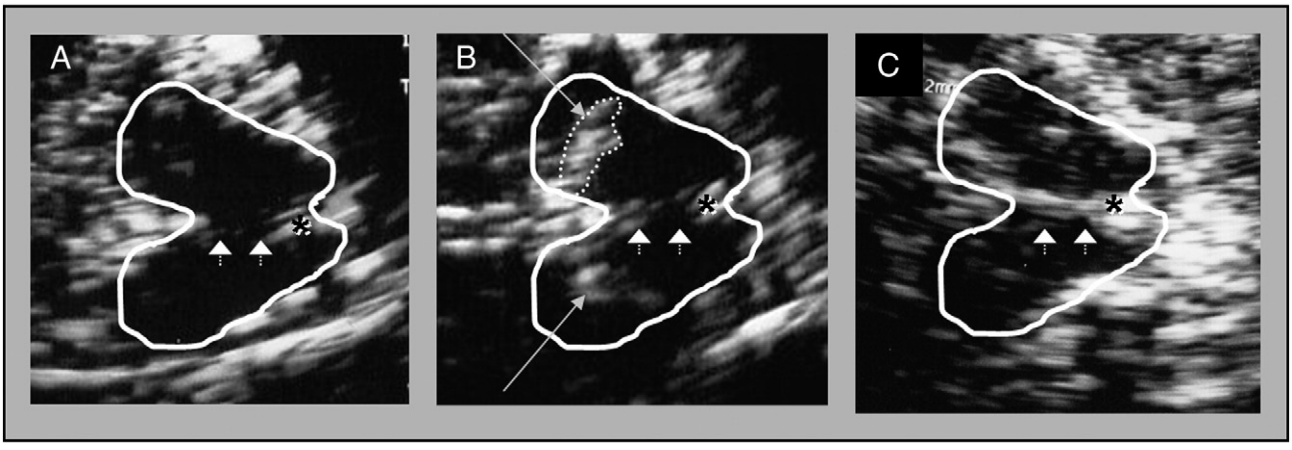

Fig. 1. Corresponding mesencephalic axial examination planes in three patients with bipolar disorder. The butterfly-shaped midbrain encircled for better visualisation. Black star marks the aqueduct. Arrowheads indicate the brainstem raphe. (A) raphe structure not visible, Grade 0, pathologic finding. (B) slight and interrupted echogenic raphe structure, Grade 1, pathologic finding. (C) normal echogenicity, Grade 2, normal finding. Note the marked bilateral hyperechogenicity of the substantia nigra in the second patient (arrows in B). Echogenic area of the right substantia nigra was encircled for computerized planimetric measurement.

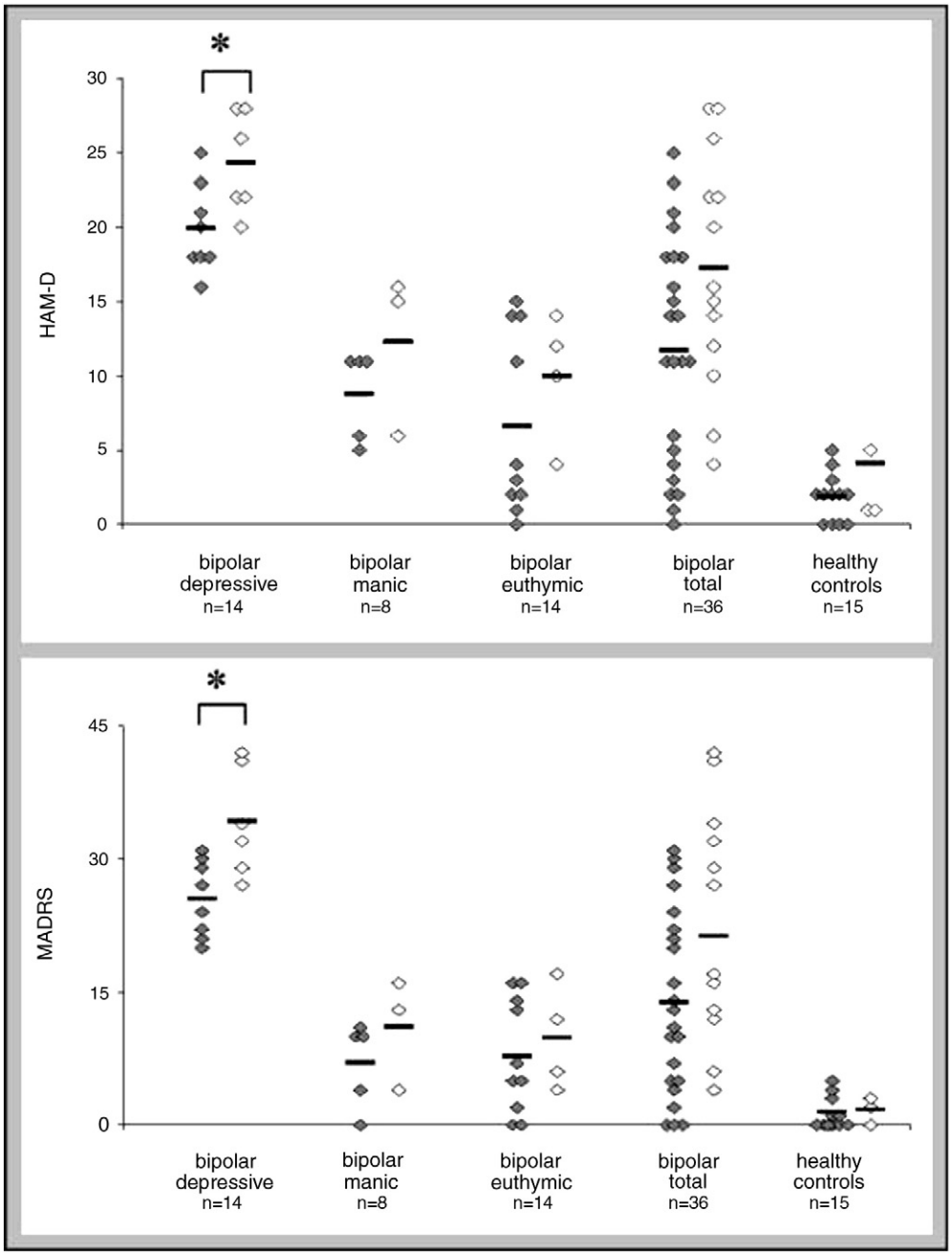

Fig. 2. Intra-subgroup comparison of subjects with normal and with pathologic raphe echogenicity. Gray dots = subjects with normal raphe echogenicity (Grade 2). White dots = subjects with pathologic raphe echogenicity (Grade 0 and Grade 1). Black bar = mean. * = $p<0.05$. Within the bipolar depressive group, pathologic findings of BR correlated significantly with the severity of depressive symptoms estimated by the scores of HAM-D and MADRS ($p=0.029$ and $p=0.020$ respectively).

that this finding is based on increased amounts of iron, bound to proteins other than ferritin and not to the progressive neurodegeneration in the SN (Berg et al., 2002; Spiegel et al., 2006). Although these data are characteristic for idiopathic Parkinson's disease, hyperechogenicities of the SN have also been, albeit less frequently, in other extrapyramidal movement disorders, such as spinocerebellar ataxia, corticobasal degeneration and Huntington's disease (Postert et al., 1999, 2004; Walter et al., 2004). Beyond this field of neurological movement disorders, SN hyperechogenicites have been reported also in depressive disorders, indicating a possible marker of an underlying dopamine dysregulation in the pathogenesis of depression (Walter et al., 2007b). A cyclical dysregulation in quantitative dopaminergic transmission is increasingly discussed as an underlying model in the pathophysiology of bipolar disorder (Berk et al., 2007). In animal models of bipolar disorder, psychostimulants causing an excessive dopamine neurotransmission are used to induce manic symptoms (Machado-Vieira et al., 2004). Psychostimulants like amphetamine also induce manic reactions in humans, which are regularly followed by depressive symptoms in the wearing-off phase (Berk et al., 2007). Such cyclical mood and behavioural disturbances are also observed in patients with Parkinson's disease receiving dopamine replacement therapies (Evans and Lees, 2004). In bipolar patients, amphetamine abuse is documented to worsen the course and outcome of the disease (Goldberg et al., 1999). Furthermore, dopamine agonists like bromocriptine may also induce manic symptoms in bipolar patients (Gerner et al., 1976), while dopamine antagonists are effective in antimanic treatment (Tohen et al., 2003).

Table 4
Evaluation of brain parenchyma echogenicities in different subgroups of patients with bipolar disorders.

Structure	Bipolar depressed, $n=14$	Bipolar manic, $n=8$	Bipolar euthym, $n=14$	Significance
Width of third ventricle, mm				$p=0.138$[a]
	2.9 ± 1.3	4.7 ± 2.2	4.2 ± 2.4	(n.s.)
	(1.7–6.5)	(2.7–8.7)	(1.3–10.1)	$H=3.98$
				$d.f.=2$
Substantia nigra (SN)	Normal: 9 (64.3%)	Normal: 8 (100%)	Normal: 13 (92.9%)	
	Hyperechogenic: 5 (35.7%)	Hyperechogenic: 0 (0.0%)	Hyperechogenic: 1 (7.1%)	$p=0.069$[b]
	Moderate: 2; marked: 3	Moderate: 0; marked: 0	Moderate: 0; marked: 1	(n.s.)
	UL: 2 BL: 0; UL: 1 BL: 2	UL: 0 BL: 0; UL: 0 BL: 0	UL: 0 BL: 0; UL: 1 BL: 0	$d.f.=2$
Area of SN hyperechogenicity (cm^2)				$p=0.802$[a]
	0.11 ± 0.13	0.05 ± 0.07	0.07 ± 0.10	(n.s.)
	(0.00–0.32)	(0.00–0.17)	(0.00–0.33)	$H=0.44$
				$d.f.=2$
Caudate nucleus	Normal: 13 (92.9%)	Normal: 7 (100%)[c]	Normal: 12 (85.7%)	$p=0.790$[b]
	Hyperechogenic: 1 (7.1%)	Hyperechogenic: 0 (0.0%)[c]	Hyperechogenic: 2 (14.3%)	(n.s.)
	UL: 1 BL: 0	UL: 0 BL: 0; UL: 0 BL: 0	UL: 1 BL: 1	$d.f.=2$
Lentiform nucleus	Normal: 13 (92.9%)	Normal: 7 (100%)[c]	Normal: 11 (78.6%)	$p=0.501$[b]
	Hyperechogenic: 1 (7.1%)	Hyperechogenic: 0 (0.0%)[c]	Hyperechogenic: 3 (21.4%)	(n.s.)
	UL: 1 BL: 0	UL: 0 BL: 0; UL: 0 BL: 0	UL: 1 BL: 2	$d.f.=2$
Mesencephalic raphe	Normal: 8 (57.1%)	Normal: 5 (62.5%)	Normal: 10 (71.4%)	$p=0.684$[b]
	Hypoechogenic: 6 (42.9%)	Hypoechogenic: 3 (37.5%)	Hypoechogenic: 4 (28.6%)	(n.s.)
	Reduced: 5; not visible: 1	Reduced: 2; not visible: 1	Reduced: 3; not visible: 1	$d.f.=2$

UL = unilateral; BL: bilateral.
[a] Kruskal–Wallis test (n.s. = not significant).
[b] Freeman–Halton extension of the Fisher exact test (n.s. = not significant).
[c] Evaluation performed only in 7 of the 8 bipolar manic patients.

In the discussed cyclic dopamine dysfunction model, depressive symptoms are assigned to be in the context of lowered dopamine transmission. Congruently, the dopamine agonist pramipexole has been effective in the treatment of depressive episodes (Ostow, 2002). With regard to the pharmacology of mood stabilizers, modulation of dopamine transmission may be one important aspect, particularly since a decrease of dopaminergic transmission has been reported for carbamazepine and valproate as well as for lithium (Berk et al., 2007).

There are only a few brain imaging studies investigating the dopaminergic pathways in bipolar disorders. In one single photon emission computed tomography (SPECT) study, the decrease in striatal iodobenzamide binding after amphetamine challenge did not differ between bipolar patients and healthy controls (Anand et al., 2000). As transcranial sonography and SPECT disclose complementary aspects of dopamine dysfunction in patients with Parkinson's disease, it is conceivable that this observation is transferable to bipolar disorders (Spiegel et al., 2006). Nevertheless, no SN hyperechogenicities were observed in our patient collective. In the depressed subgroup of the patients, a higher prevalence of SN hyperechogenicities was seen, but this trend did not reach statistical significance.

With regard to echogenicity of brainstem raphe, no significant differences were seen between bipolar patients and the control group. Our findings confirm the sole report about about BR echogenicity in bipolar disorder, where no accumulated hypoechogenicity of BR was seen (Becker et al., 1995a). Using a 4-point scale (not visible, reduced, normal and increased echogenicity) in the classification of BR structures, Becker et al. reported even an increase of BR echogenicity in bipolar patients compared to healthy controls. Since the first consensus meeting on TCS of the European Society of Neurosonology and Cerebral Hemodynamics in 2001, a 3-point scale (not visible, reduced and normal echogenicity) has been recommended for the classification of BR echogenicity, so that actual and previous results are not matchable one-to-one (Walter et al., 2007a). BR hypoechogenicity is a frequent and characteristic finding in patients with unipolar depression as well as in depressed patients with Parkinson's and Huntington's disease (Becker et al., 1995a; Berg et al., 1999; Walter et al., 2007b, c; Krogias et al., 2011). The precise pathophysiological and morphological interpretation of BR hypoechogenicity is still speculative. A correlation of this finding to signal alteration on MRI studies has been reported previously, suggesting that hypoechogenicity reflects a structural disruption of mesencephalic raphe structures (Becker et al., 2001). Congruently to the findings of Becker et al., we could also document similar frequencies of BR hypoechegenicity in bipolar patients and in healthy controls (Becker et al., 1995a). Furthermore, no significant differences were seen between the different conditions of the disease (Table 4). In contrast to unipolar depression, sonographic findings of bipolar patients may indicate a structural integrity of BR structures.

On the other hand, raphe hypoechogenicities have also been reported in patients with adjustment disorder with depressed mood, suggesting that this finding reflects a predisposition for depressive reaction (Walter et al., 2007c). Interestingly, bipolar depressive patients in our study with reduced BR echogenicity showed higher scores on the HAM-D scores in HAM-D and MADRS than patients with normal echogenic BR (Fig. 2), suggesting that depressive symptoms are more severe if the bipolar disorder coexists with a structural predisposition for depression. Further multimodal imaging studies are needed to elucidate the pathogenesis of the basal ganglia echogenicities in depression. In clinical practice, TCS findings might be useful as an additional diagnostic tool for the differentiation of bipolar and unipolar patients.

The most consistently documented neuroanatomic abnormalities in adult patients with bipolar disorder are lateral ventricle enlargement (+17%) and increased rates of deep white matter hypersintensities (Bearden et al., 2010). Regarding brain atrophy, MRI studies documented a slight but significant ventriculomegaly in patients with bipolar disorder (Strakowski et al., 2002). The sonographic evaluation of the ventricular system including ventricular enlargement has been described previously (Seidel et al., 1995). Since the width of the third ventricle serves as a marker of cerebral atrophy in the sonographic discrimination of corticobasal degeneration and progressive supranuclear palsy, we used this parameter for statistical analysis (Walter et al., 2004). The depicted widths of the third ventricle of bipolar patients in our study were below the cut-off value of 7–10 mm evaluated in neurological studies (Walter et al., 2007a). However, bipolar patients in our study showed significantly larger widths of the third ventricle than the control group (Table 3). Further longitudinal TCS studies are needed to investigate if the observed slight enlargement of the third ventricle occurs at illness onset or progresses during the course of the disease.

At present, there: is substantial inconsistency in results of structural MRI studies in adult bipolar disorder (Haldane and Frangou, 2004). This is likely consequent upon the limited statistical power of the studies, together with their clinical and methodological heterogeneity, e.g., in the recent large international mega-analysis of data with bipolar patients (Hallahan et al., 2010). Functional imaging studies exhibited a lack of activation in parts of the network of the prefrontal cortex, the anterior cingulate cortex (ACC) and the precuneus (Malhi et al., 2008). Notably, the insula and temporoparietal junction demonstrated a lack of activation. Consequently, patients with bipolar disorder are impaired concerning social cognition and theory of mind (Wolf et al., 2010). Our data are a further mosaic stone in the complex neural network impaired in bipolar disorders. The role of the mesencephalic raphe nuclei remains unclear. Further studies are necessary.

There are some limitations in our study. The small sample sizes of the subgroups do not enable a meaningful investigation of the effect of the existent diverse medication. Bipolar disorder is a complex disease entity, so that not only dopamine and serotonin but other neurotransmitters, as well as second messenger systems, have well-documented roles. The dopaminergic and serotonergic systems are also complex, so that a statement about the functioning of these systems cannot be restricted to the some few sections. Furthermore, due to the composition of the control sample, the control group is not fully representative of the population from which the patient sample was drawn.

Moreover, there are some general limitations of transcranial sonography, which need to be taken into account. Due to insufficient transtemporal bone window, in 5–10% of white individuals the midbrain structures are only partially assessable (Berg et al., 2008). In addition, the area that can be evaluated is limited to deep grey matter structures, so that other relevant structures like cortical regions are excluded from the examination. Moreover, the reliability of the findings is dependent on the quality of the ultrasound system as well as on the qualification of the investigator.

In conclusion, our study reveals a regular pattern of cerebral echogenicities in bipolar disorder. This is different from findings in unipolar depression. Additionally, a relationship between the severity of depressive symptoms and BR hypoechogenicity could be identified in the bipolar depressive group. Furthermore, the width of the third ventricle was significantly larger in the patient group. This is in accordance to MRI studies reporting a relative ventriculomegaly in bipolar patients.

TCS is a commonly available, non-invasive and inexpensive diagnostic tool, which provides reliable information about the morphology and function of the brain in bipolar disorder, even in agitated patients who do not tolerate other imaging techniques. Walter et al. demonstrated in a phantom study that if the requirements for optimal TCS image resolution are fulfilled, i.e. sufficient acoustic bone window, increased echogenicity of target structure and its localization in a distance of maximum ± 15 mm from the midsagittal plane, findings suggest that contemporary TCS systems achieve higher image resolution of intracranial structures in comparison not only to older generation systems, but also to MRI under clinical conditions (Walter et al., 2008). The predominant justification for the additional use of TCS in brain imaging is that due to the different underlying physical approaches, TCS reveals abnormalities that are not detected in routine structural neuroimaging methods like MRI or cCT.

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