

Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders

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Substantia nigra (SN) hyperechogenicity is a characteristic transcranial sonography (TCS) finding in idiopathic Parkinson's disease. SN hyperechogenicity, found also in ~10% of healthy adults, was related to a subclinical malfunction of the nigrostriatal dopaminergic system on PET studies and is, therefore, thought to represent a risk marker for Parkinson's disease. Epidemiological findings suggest an increased risk in subjects with depression. To find out whether frequency of SN hyperechogenicity is increased in depression, we performed TCS of brainstem and basal ganglia in 200 subjects: 55 controls without depression and without Parkinson's disease, 55 subjects with depression without Parkinson's disease (D^+PD^-), 45 Parkinson's disease patients without depression (D^-PD^+) and 45 Parkinson's disease patients with depression (D^+PD^+). Marked SN hyperechogenicity was found in 13% of controls, 40% of D^+PD^- (χ^2 test, $P=0.001$), 69% of D^-PD^+ (vs D^+PD^- , $P=0.004$) and 87% of D^+PD^+ patients (vs D^-PD^+ , $P=0.04$). Reduced echogenicity of brainstem raphe, thought to reflect alteration of the serotonergic system, was more frequent in depressed than in non-depressed subjects, irrespective of presence of Parkinson's disease, confirming earlier reports. The combined finding of marked SN hyperechogenicity and reduced raphe echogenicity in Parkinson's disease patients, however, was clearly associated with a history of depression prior to Parkinson's disease onset, whereas in D^+PD^- patients this combined TCS abnormality was related to motor asymmetry. In D^+PD^+ patients with depression prior to Parkinson's disease onset ($n=12$), larger SN echogenic sizes correlated with younger age at Parkinson's disease onset (Spearman test, $r=-0.607$, $P=0.036$). TCS findings of other basal ganglia did not differ between the groups studied. Data suggest that in subjects with depression nigrostriatal vulnerability is frequent, and that TCS might be useful to detect individuals at risk for developing Parkinson's disease.

Keywords: transcranial sonography; major depression; adjustment disorder with depressed mood; Parkinson's disease; substantia nigra

Abbreviations: SN = substantia nigra; TCS = transcranial sonography

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Introduction

Depression is a frequent comorbid condition in Parkinson's disease (Cummings, 1992). In a review of all studies of depression in Parkinson's disease published from 1992 to 1998, comprising a total of 5911 Parkinson's disease patients, 31% of patients were, at any given time, depressed (Brooks and Doder, 2001). Several reports indicate that depression may precede the diagnosis of Parkinson's disease (Mayeux *et al.*, 1981; Nilsson *et al.*, 2001; Schuurman *et al.*, 2002; Leentjens *et al.*, 2003). In large register studies, each spanning 15–16 years, the risk for depressed patients for developing Parkinson's disease was 2.2–3.1-fold compared

to non-depressed controls (Nilsson *et al.*, 2001; Schuurman *et al.*, 2002; Leentjens *et al.*, 2003). These studies suggest that either depression is an early symptom of Parkinson's disease or that depression is associated with a risk factor for Parkinson's disease (Lieberman, 2006).

Transcranial sonography (TCS) has proved reliable and sensitive in detecting basal ganglia abnormalities, e.g. of substantia nigra (SN) in idiopathic Parkinson's disease and of lenticular nucleus in atypical parkinsonian syndromes (Becker *et al.*, 1995a; Berg *et al.*, 2001a; Walter *et al.*, 2002, 2003, 2004a). In more than 90% of Parkinson's disease

patients, TCS reveals characteristic SN hyperechogenicity, which is stable during the course of the disease and is thought to reflect increased amounts of iron, bound to proteins other than ferritin, but not the progressive neurodegeneration in the SN (Berg *et al.*, 2001a, 2002, 2005; Walter *et al.*, 2002, 2003; Spiegel *et al.*, 2006). Marked SN hyperechogenicity is also found in 10% of healthy adults aged between 20 and 80 years, and has been related to a functional impairment of the nigrostriatal dopaminergic system (Berg *et al.*, 1999a, 2001b; Walter *et al.*, 2004b). Therefore, SN hyperechogenicity has been proposed to indicate an increased risk for developing Parkinson's disease (Berg *et al.*, 1999a, 2002) or a subclinical stage of the disease (Walter *et al.*, 2004b).

To further test the hypothesis that depression is associated with an increased risk for Parkinson's disease, we studied the frequency of SN hyperechogenicity in patients with depression. For this, patients with depressive states without and with concomitant Parkinson's disease were compared with normal controls and with Parkinson's disease patients without depression.

Material and Methods

Patients

Altogether 200 subjects were studied: 55 non-parkinsonian patients with depressive disorder (D^+PD^-), 55 age-matched controls without any psychiatric or neurodegenerative disorder (D^-PD^-), 45 Parkinson's disease patients with concomitant depression (D^+PD^+) and 45 Parkinson's disease patients without depression (D^-PD^+). Table 1 shows their demographic data.

Fifty-five D^+PD^- patients treated at the Department of Psychiatry and Psychotherapy of the University of Rostock were eligible for inclusion. Inclusion criteria were (i) present inpatient treatment of current depressive symptoms, (ii) the unequivocal classification of a depressive state according to DSM-IV diagnostic categories as specified later (American Psychiatric Association, 1994) and (iii) transcranial insonability. Exclusion criteria were

(i) symptomatic psychic disorders, (ii) depression with psychotic symptoms, (iii) other psychotic or schizophrenic disorders, (iv) recent neuroleptic treatment or (v) recent concomitant neurological disorders. Informed consent was obtained from each patient. Following the Structured Clinical Interview for DSM-IV Axis-I Disorders (First *et al.*, 1996), 40 patients met the diagnostic criteria for major depressive disorder (MDD) and 15 for adjustment disorder with depressed mood (ADDM). The mean age of patients with MDD was 57.1 ± 12.7 years, and with ADDM 49.2 ± 11.3 years (*t*-test, $P=0.034$). All patients were on antidepressant medication. At the time of TCS, MDD (ADDM) patients had a severity of depression of 21.4 ± 12.7 (20.6 ± 7.5 ; $P=0.77$) on the Beck Depression Inventory (Beck *et al.*, 1961), and of 19.5 ± 6.9 (21.6 ± 5.8 ; $P=0.32$) on the Hamilton 21-item Depression Rating Scale (Hamilton, 1967). Severity of motor retardation on the motor part of the Unified Parkinson's disease Rating Scale (UPDRS-III) was 5.7 ± 4.6 in MDD, and 3.1 ± 2.8 in ADDM patients ($P=0.019$) (Fahn *et al.*, 1987). Motor asymmetry, defined as a right-to-left difference of side-specific scores of the UPDRS-III, was found in 21 D^+PD^- patients (17 with MDD, 4 with ADDM) none of whom fulfilled the diagnostic criteria of Parkinson's disease (Hughes *et al.*, 1992). D^+PD^- patients without and with motor asymmetry did not differ with respect to gender (χ^2 test, $P>0.4$), age (*t*-test, $P>0.4$), duration ($P>0.6$), severity ($P>0.5$) or diagnostic category of depression (χ^2 test, $P>0.2$).

All Parkinson's disease patients were treated in the movement disorder clinic at the Department of Neurology of the University of Rostock and fulfilled the British Brain Bank criteria for definite Parkinson's disease (Hughes *et al.*, 1992). Their mean age was 66.1 ± 9.7 , age at Parkinson's disease onset 58.4 ± 10.7 and Parkinson's disease duration 7.7 ± 6.4 years. At the time of TCS investigation, all patients were on sufficient antiparkinsonian medication and had a disease severity of 35.7 ± 19.7 on the UPDRS-III. All patients in group D^+PD^+ had a documented depressive syndrome fulfilling diagnostic criteria of MDD within the past 6 months and were on antidepressant medication. Twelve (27%) D^+PD^+ patients had a history of MDD prior to onset of Parkinson's disease, with a mean onset age of MDD of 48.0 ± 12.2 (range, 24–73) years and a mean latency between MDD and onset

Table 1 Demographic data of patients studied

	D^-PD^-	D^+PD^-	D^-PD^+	D^+PD^+
Number	55	55 ^a	45	45
Sex, M/F	27/28	11/44	23/22	23/22
Age, years, mean \pm SD (range)	54.9 ± 18.7 (24–81)	55.0 ± 12.7 (20–76)	67.2 ± 8.8 (35–83)	65.0 ± 10.5 (38–86)
Age at Parkinson's disease onset, years, mean \pm SD (range)	n.a.	n.a.	58.8 ± 9.8 (31–76)	57.0 ± 11.4 (34–81)
Parkinson's disease duration, years, mean \pm SD (range)	n.a.	n.a.	7.4 ± 6.4 (0.5–28)	8.1 ± 6.4 (0.5–29)
Parkinson's disease motor subtype, AR/MT/TD	n.a.	n.a.	27/13/5	27/13/5
UPDRS-III score ^b , mean \pm SD	n.d.	5.0 ± 4.3	32.4 ± 20.7	34.1 ± 18.5
BDI score ^c , mean \pm SD	n.d.	21.6 ± 10.9	n.d.	20.2 ± 4.9

D^-PD^- = control subjects without any psychiatric or neurodegenerative disorder; D^+PD^- = depressed patients without Parkinson's disease; D^-PD^+ = Parkinson's disease patients without depression; D^+PD^+ = Parkinson's disease patients with concomitant depression; AR = akinetic-rigid type Parkinson's disease; MT = mixed-type Parkinson's disease; TD = tremor-dominant Parkinson's disease; UPDRS-III = Unified Parkinson's disease Rating Scale, motor part; BDI = Beck Depression Inventory; SD = standard deviation, n.a. = not applicable, n.d. = not determined. ^a40 D^+PD^- patients had major depressive disorder and 15 adjustment disorder with depressed mood (for details, see text). ^b D^-PD^+ and D^+PD^+ patients on antiparkinsonian medication. ^c D^+PD^- and D^+PD^+ patients on antidepressant medication.

of Parkinson's disease of 7.5 ± 8.0 (range, 0.5–29) years. None of the D^-PD^+ patients had any history of MDD. Since SN echogenicity has been demonstrated to vary with age at onset and motor subtype of Parkinson's disease (Walter *et al.*, 2007), patients in groups D^-PD^+ and D^+PD^+ were matched not only by age and gender but also by age of Parkinson's disease onset and Parkinson's disease motor subtype (Table 1).

As controls (group D^-PD^-) served healthy subjects ($n=18$), patients with cardiogenic or vasogenic cerebral embolism in whom leucoencephalopathy was excluded ($n=24$), cardiogenic syncope ($n=4$), transient global amnesia ($n=2$), otogenic vertigo ($n=2$), epilepsy ($n=1$), meningioma ($n=1$) or diseases of the peripheral nervous system ($n=3$).

Transcranial brain sonography

TCS was performed through the preauricular acoustic bone windows using a colour-coded phased-array ultrasound system equipped with a 2.5-MHz transducer (Sonoline; Siemens, Erlangen, Germany). The ultrasound parameters chosen were: penetration depth 16 cm, dynamic range 50 dB, high persistence, reject 7. SN echogenic size measurements were performed on axial TCS scans automatically after manually encircling the outer circumference of SN's echogenic area. SN echogenic sizes of $<0.2 \text{ cm}^2$ are classified as normal, sizes of 0.25 cm^2 and above as markedly hyperechogenic, and sizes in-between as moderately hyperechogenic (Berg *et al.*, 1999a, 2001a; Walter *et al.*, 2002). For classification of patients with respect to their SN echogenicity the greater value of bilateral SN echogenic sizes was used. For intergroup comparisons, both SN echogenic sizes of each individual were used. Echogenicity of the brainstem raphe was rated as reduced when its structure was interrupted or not visible, i.e. isoechogenic compared with the adjacent brain parenchyma (Becker *et al.*, 1997; Berg *et al.*, 1999b). Additionally, echogenicity of thalami, lenticular nuclei and heads of caudate nuclei was investigated and classified as hyperechogenic when it was more

intense than the surrounding white matter (Walter *et al.*, 2002, 2003, 2004a). Classification of patients with respect to echogenicity of lenticular nucleus, caudate nucleus and thalamus was based on the most affected side of the investigated brain structure. Widths of third ventricle and of frontal horns of lateral ventricles were measured on a standardized diencephalic axial scanning plane. All TCS examinations were performed by one experienced sonographer (U.W.) who was blinded to the clinical data of the patients. The individuals of groups D^+PD^- and D^-PD^- underwent a second TCS examination on the same day, performed by an independent sonographer (L.M., S.H.). TCS images of brain structures of all Parkinson's disease patients were stored and off-line analysed by a second investigator blind to clinical data. A structure was only regarded as abnormal on TCS, if the findings of both investigators agreed.

Statistics

Descriptive statistics are given as median with lower (25th percentile) and upper (75th percentile) quartile. Since SN echogenic sizes were not normally distributed, as demonstrated by the Shapiro–Wilks test, for group comparison of SN echogenic sizes the Mann–Whitney U test was used. Categorical data were analysed by χ^2 test. Comparison of means was performed with the t -test for independent samples. For comparison of echogenic sizes and of ventricle widths with age, age at disease onset, disease duration and clinical scores the Spearman correlation test was used. Interrater reliability was assessed by the Spearman correlation test (SN echogenic sizes) and by Cohen's kappa (Brainstem raphe echogenicity scores).

Results

TCS findings of SN, brainstem raphe, lenticular nucleus and caudate nucleus in the different groups studied are summarized in Table 2. SN and brainstem raphe were

Table 2 Qualitative assessment of brain parenchyma echogenicity of brainstem raphe, substantia nigra, lenticular nucleus and caudate nucleus in normal subjects without depression and without Parkinson's disease [D^-PD^-], in depressed patients without Parkinson's disease [D^+PD^-] and in Parkinson's disease patients without [D^-PD^+] and with [D^+PD^+] concomitant depression

Structure	Brain parenchyma echogenicity					
	Group D^-PD^- $n=55$	Group D^+PD^- $n=55$	Significance ^a	Group D^-PD^+ $n=45$	Group D^+PD^+ $n=45$	Significance ^a
Substantia nigra						
Normal echogenicity	40 (73)	19 (35)		2 (4)	0 (0)	
Moderate hyperechogenicity ^b	8 (14)	14 (25)	n.s.	12 (27)	6 (13)	n.s.
Marked hyperechogenicity ^b	7 (13)	22 (40)	$P=0.001$	31 (69)	39 (87)	$P=0.043$
Brainstem raphe						
Normal echogenicity	50 (91)	26 (47)		38 (84)	28 (62)	
Reduced echogenicity ^c	5 (9)	29 (53)	$P<0.001$	7 (16)	17 (38)	$P=0.017$
Lenticular nucleus^d						
Normal echogenicity	49 (89)	39 (78)		36 (90)	35 (83)	
Hyperechogenicity ^e	6 (11)	11 (22)	n.s.	4 (10)	7 (17)	n.s.
Caudate nucleus^d						
Normal echogenicity	51 (93)	42 (84)		32 (80)	37 (88)	
Hyperechogenicity ^e	4 (7)	8 (16)	n.s.	8 (20)	5 (12)	n.s.

Classifications were based on the most affected side; percentages are given in brackets. χ^2 test (n.s. = not significant). Hyperechogenicity as determined by substantia nigra size (see section Material and Methods). Reduced echogenicity as determined by visibility of brainstem raphe (see section Material and Methods). 5 D^+PD^- patients, 5 D^-PD^+ patients and 3 D^+PD^+ patients not evaluated due to insufficient temporal acoustic bone windows. Hyperechogenicity as determined by structure visibility (see section Material and Methods).

evaluated in all patients, whereas in five D^+PD^- patients, five D^-PD^+ patients and three D^+PD^+ patients lenticular and caudate nuclei were not assessable due to insufficient temporal acoustic bone windows.

Substantia nigra echogenicity

Typical sonographic images of normal and hyperechogenic SN are shown in Fig. 1. Figure 2 shows the frequency of SN hyperechogenicity in groups D^-PD^- , D^+PD^- , D^-PD^+ and D^+PD^+ . Sonographic measurements of SN echogenic sizes (performed by a second sonographer in groups D^-PD^- and D^+PD^-) proved adequately reproducible considering the smallness of structure measured (Spearman correlation, $r=0.77$, $P<0.001$). The median SN echogenic size (including bilateral measurements) of the controls (group D^-PD^-) was 0.14 (0.11; 0.18) cm^2 , and of depressive patients without Parkinson's disease (D^+PD^-) was 0.20 (0.15; 0.26) cm^2 (Mann–Whitney U test, $P<0.001$). In group D^+PD^- , no difference of SN echogenic sizes was found between patients with MDD and those with ADDM ($P=0.37$). The median SN echogenic size in D^-PD^+ patients was 0.25 (0.22; 0.32) cm^2 (compared with group D^-PD^- : $P<0.001$; D^+PD^- : $P<0.001$) and in D^+PD^+ patients 0.27 (0.24; 0.31) cm^2 (compared with group D^-PD^- : $P<0.001$; D^+PD^- : $P<0.001$; D^-PD^+ : $P=0.10$). The frequency of patients with marked SN hyperechogenicity increased significantly in group D^+PD^- (40%) compared with group D^-PD^- (13%; χ^2 test, $P=0.001$), in group D^-PD^+ (69%) compared with group D^+PD^- ($P=0.004$) and in group D^+PD^+ (87%) compared with group D^-PD^+ ($P=0.04$) (Fig. 2). Within group D^+PD^- , marked SN hyperechogenicity was found with same frequency in patients with MDD and with ADDM

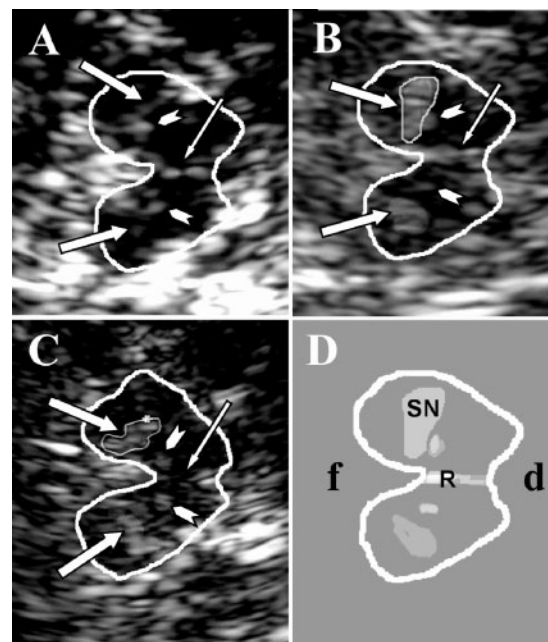


Fig. 1 Sonographic images of corresponding midbrain axial sections in three subjects. The butterfly-shaped midbrain was encircled for better visualization. Thick arrows indicate bilateral substantia nigra; thin arrow, brainstem raphe; arrowheads, bilateral red nuclei. (A) Subject with normal, nearly invisible substantia nigra and normal, highly echogenic brainstem raphe. (B) Subject with marked bilateral hyperechogenicity of the substantia nigra but normal, highly echogenic brainstem raphe. Echogenic area of the right substantia nigra was encircled for computerized measurement. (C) Subject with marked bilateral hyperechogenicity of the substantia nigra and abnormal, reduced echogenicity of the brainstem raphe. Echogenic area of the right substantia nigra was encircled for computerized measurement. (D) Schematic illustration of (B): within the encircled midbrain axial section, bilateral SN, red nuclei and brainstem raphe (R) are highlighted.

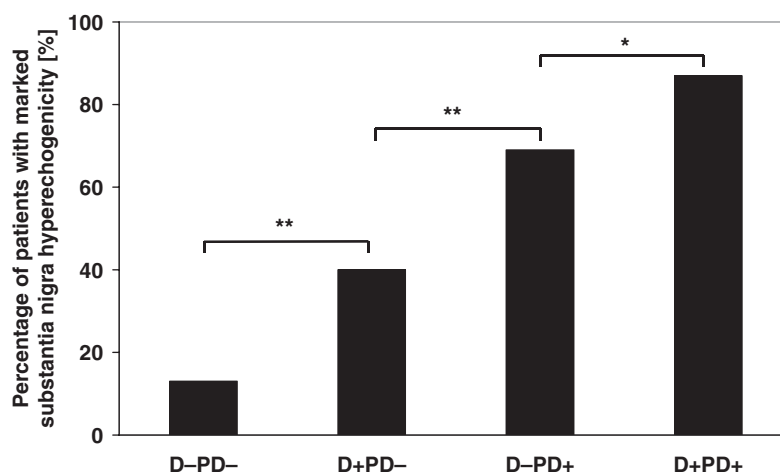


Fig. 2 Diagram showing the frequency of marked SN hyperechogenicity, detected with transcranial sonography, in 55 non-depressed non-parkinsonian controls (D^-PD^-), 55 depressed subjects without Parkinson's disease (D^+PD^-), 45 non-depressed Parkinson's disease patients (D^-PD^+) and 45 depressed Parkinson's disease patients (D^+PD^+). Out of group D^+PD^- , 40 had major depressive disorder and 15 adjustment disorder with depressed mood in whom frequency of SN hyperechogenicity did not differ (each, 40%). Note that non-parkinsonian subjects with depression had a 3-fold higher frequency of SN hyperechogenicity compared to normal controls. ** $P<0.005$, * $P<0.05$ (χ^2 test).

(each, 40%). Frequency of moderate SN hyperechogenicity did not differ between groups (each comparison, $P > 0.1$). Larger SN echogenic size of each individual did not correlate with severity of depression as measured on the BDI, either in group D^+PD^- or in group D^+PD^+ (Spearman test, each, $P > 0.2$). Also, there was no correlation of larger SN echogenic size with severity of motor symptoms as measured on the UPDRS-III in either group (each, $P > 0.2$). UPDRS-III scores in D^+PD^- patients with marked SN hyperechogenicity (5.8 ± 4.3) did not differ from scores in D^+PD^- patients without marked SN hyperechogenicity (4.4 ± 4.3 ; t -test, $P = 0.24$). No correlation was found between SN echogenic size and Parkinson's disease duration in groups D^-PD^+ and D^+PD^+ . However, in group D^+PD^+ , larger SN echogenic size correlated significantly with younger age at onset of Parkinson's disease (Spearman test, $r = -0.364$, $P = 0.014$), whereas no such correlation was found in group D^-PD^+ ($P > 0.4$). This correlation was stronger if only D^+PD^+ patients with onset of depression prior to onset of Parkinson's disease were analysed ($r = -0.607$, $P = 0.036$) (Fig. 3).

Brainstem raphe echogenicity

The interrater reliability of brainstem raphe TCS (performed by a second sonographer in groups D^-PD^- and D^+PD^-) was high (Cohen's kappa 0.88, $P < 0.001$). The frequency of patients with reduced echogenicity of brainstem raphe was higher in group D^+PD^- compared with group D^-PD^- , and in group D^+PD^+ compared with group D^-PD^+ (Table 2, Fig. 4), but did not differ between groups D^-PD^- and D^-PD^+ (χ^2 test, $P = 0.32$)

nor between groups D^+PD^- and D^+PD^+ ($P = 0.14$). Within group D^+PD^- , reduced echogenicity of brainstem raphe was found with same frequency in patients with MDD (52%) and with ADDM (53%). Patients with normal and reduced echogenicity of brainstem raphe did not differ with respect to severity of depression as measured on the BDI, neither in group D^+PD^- nor in group D^+PD^+ (t -test, each, $P > 0.2$). Also, there was no correlation between brainstem raphe echogenicity and UPDRS-III scores in either group (each, $P > 0.2$). No correlation was found between brainstem raphe echogenicity and age, age at Parkinson's disease onset or Parkinson's disease duration in groups D^-PD^+ and D^+PD^+ . D^+PD^+ patients with onset of depression prior to onset of Parkinson's disease, however, exhibited reduced echogenicity of brainstem raphe in combination with marked SN hyperechogenicity more frequently (58%) than D^+PD^+ patients with later onset of depression (21%; χ^2 test, $P = 0.017$) (Fig. 5), whereas frequency of marked SN hyperechogenicity did not differ ($P = 0.55$). The combination of reduced echogenicity of brainstem raphe and marked SN hyperechogenicity was even less frequent in D^-PD^+ patients (13%, $P = 0.001$) and was not found in group D^-PD^- . Out of group D^+PD^- , patients with a combination of reduced brainstem raphe echogenicity and marked SN hyperechogenicity ($n = 11$) had more frequently a difference of UPDRS scores between the right and left side (73%) than patients without combination of these TCS abnormalities (39%; $P = 0.046$) (Fig. 5), whereas abnormal TCS of brainstem raphe or SN alone was not associated with asymmetric UPDRS scores. D^+PD^- patients with and without combination of these

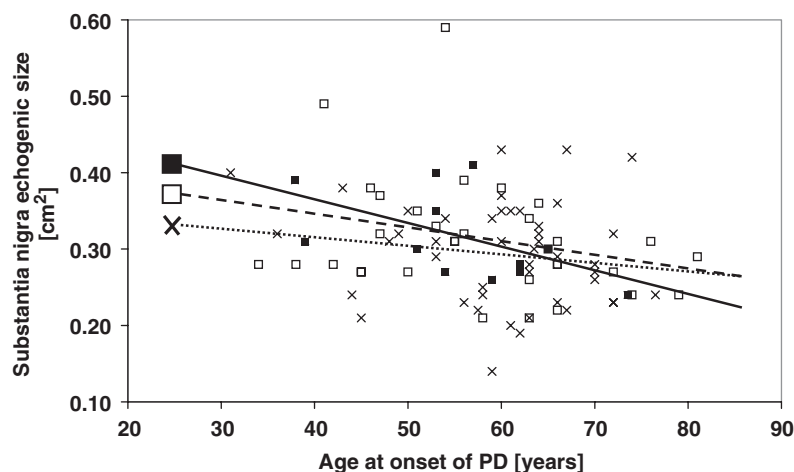


Fig. 3 Correlation between SN echogenic size in Parkinson's disease patients and age at onset of Parkinson's disease. After bilateral measurement, the larger individual SN echogenic size was used; shown are data of Parkinson's disease patients without depression (x), Parkinson's disease patients with depression after Parkinson's disease onset (open square) and Parkinson's disease patients with depressive disorder prior to Parkinson's disease onset (closed square). SN echogenic size was negatively correlated with age at onset of Parkinson's disease in the group of all depressed Parkinson's disease patients (Spearman test, $r = -0.36$, $P = 0.014$), and even stronger if only Parkinson's disease patients with history of depression prior to Parkinson's disease onset were considered ($r = -0.61$, $P = 0.036$; continuous line) but not if only Parkinson's disease patients with onset of depression after Parkinson's disease onset ($r = -0.28$, $P = 0.111$; dashed line). No correlation between SN echogenic sizes and age of Parkinson's disease onset was found in Parkinson's disease patients without depression ($P > 0.4$; dotted line).

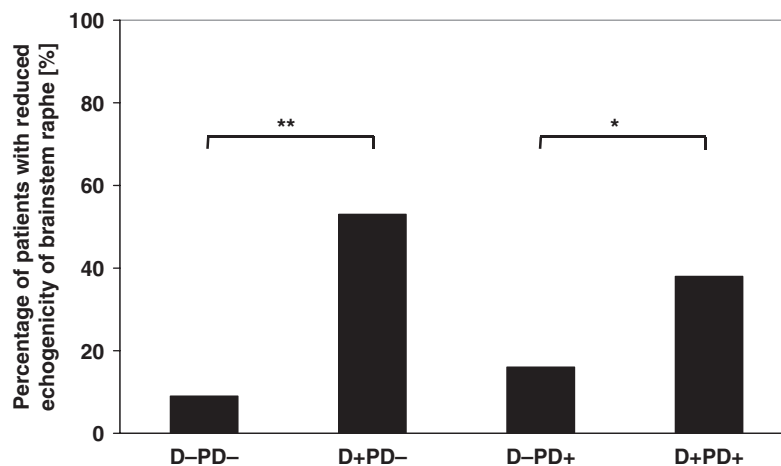


Fig. 4 Diagram showing the frequency of reduced echogenicity of brainstem raphe on transcranial sonography, in 55 non-depressed non-parkinsonian controls (D^-PD^-), 55 depressed subjects without Parkinson's disease (D^+PD^-), 45 non-depressed Parkinson's disease patients (D^-PD^+) and 45 depressed Parkinson's disease patients (D^+PD^+). Out of group D^+PD^- , 40 had major depressive disorder and 15 adjustment disorder with depressed mood in whom frequency of reduced raphe echogenicity did not differ (52%, 53%). Note that frequency of reduced raphe echogenicity is increased in depressed patients, irrespective of presence of Parkinson's disease. $**P < 0.001$, $*P < 0.05$ (χ^2 test).

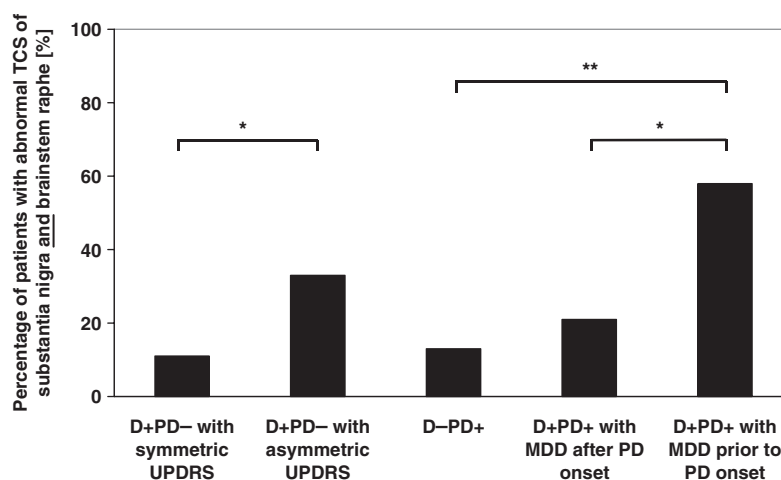


Fig. 5 Diagram showing the frequency of the combined presence of marked substantia nigra hyperechogenicity and reduced echogenicity of brainstem raphe on TCS, in 24 depressed patients without Parkinson's disease (D^+PD^-) who showed right-to-left motor asymmetry on the Unified Parkinson's disease Rating Scale, 28 D^+PD^- patients without motor asymmetry, 45 Parkinson's disease patients without depression (D^-PD^+), 33 Parkinson's disease patients with depression (D^+PD^+) with onset of major depressive disorder after Parkinson's disease onset and 12 D^+PD^+ patients with a history of major depressive disorder prior to Parkinson's disease onset. The combined sonographic abnormality was clearly associated with a history of depression prior to Parkinson's disease onset in Parkinson's disease patients, and with motor asymmetry in non-parkinsonian subjects with depression. $**P < 0.005$, $*P < 0.05$ (χ^2 test).

TCS abnormalities, however, did not differ with respect to gender (χ^2 test, $P = 0.9$), age (t -test, $P = 0.3$), duration ($P = 0.6$), severity ($P = 0.6$) or diagnostic category of depression (χ^2 test, $P = 0.4$). Combination of normal raphe echogenicity and marked SN hyperechogenicity was more frequent in Parkinson's disease patients (D^-PD^+ , D^+PD^+ , each group, 56%) than in groups D^-PD^- (13%, $P < 0.001$) and group D^-PD^+ (20%, $P < 0.001$) but did not differ between groups D^-PD^- and D^+PD^- ($P = 0.30$).

Other TCS findings

Caudate nucleus hyperechogenicity was more frequent in group D^-PD^+ compared with group D^-PD^- but the difference failed statistical significance (χ^2 test, $P = 0.065$). No differences were found if other groups were compared. Lenticular nucleus hyperechogenicity was detected with similar frequency in all groups studied. There was no correlation between clinical scores (BDI, UPDRS-III) and echogenicity of caudate or lenticular nucleus.

Mean width of third ventricle did not differ between patients of group D⁻PD⁻ (5.3 ± 3.1 mm) and those of group D⁺PD⁻ (4.6 ± 2.1 mm, *t*-test, *P* = 0.13) nor between patients of group D⁻PD⁺ (7.4 ± 2.5 mm) and those of group D⁺PD⁺ (6.7 ± 2.5 mm, *P* = 0.20), but was larger in Parkinson's disease patients compared to non-parkinsonian subjects (*P* < 0.001). Mean width of frontal horns did not differ between patients of group D⁻PD⁻ (14.1 ± 3.5 mm) and those of group D⁺PD⁻ (13.3 ± 2.3 mm, *P* = 0.19) nor between patients of group D⁻PD⁺ (16.2 ± 3.6 mm) and those of group D⁺PD⁺ (14.9 ± 2.9 mm, *P* = 0.08), but was larger in Parkinson's disease patients compared to non-parkinsonian subjects (*P* < 0.01).

Discussion

TCS data obtained in this study show that the finding of SN hyperechogenicity, which is characteristic for idiopathic Parkinson's disease, is also frequent in patients with depressive disorders. In non-parkinsonian subjects with depression, marked SN hyperechogenicity is found with a 3-fold frequency compared to the age-matched normal population. Reduced echogenicity of brainstem raphe is more frequent in depressed than in non-depressed patients, irrespective of presence of Parkinson's disease. The combination of marked SN hyperechogenicity and reduced raphe echogenicity, however, is significantly associated with a history of depressive disorder prior to onset of Parkinson's disease in Parkinson's disease patients, and with motor asymmetry in non-parkinsonian subjects with depression. In Parkinson's disease patients with depression prior to onset of Parkinson's disease, larger SN echogenic sizes were clearly correlated with earlier onset of Parkinson's disease. TCS abnormalities of caudate and lenticular nucleus were found with similar low frequency in all groups studied.

The found frequency of marked SN hyperechogenicity in Parkinson's disease patients and normal controls is in line with earlier reports (Berg *et al.*, 2001a; Walter *et al.*, 2002, 2003, 2007). This TCS feature is highly characteristic for idiopathic Parkinson's disease and correlates with younger age at Parkinson's disease onset, but does not change in the course of the disease (Berg *et al.*, 2001a, 2005; Walter *et al.*, 2007). Moreover, SN echogenicity in Parkinson's disease patients does not correlate with the degeneration of nigrostriatal dopaminergic neurons as measured with SPECT (Spiegel *et al.*, 2006). SN hyperechogenicity in Parkinson's disease must therefore be regarded as a trait marker featuring the predisposition for the disease rather than a severity marker reflecting changes in SN architecture due to proceeding cell loss or continuous accumulation of toxic substances according to disease progression over time. Only 1–2% of subjects older than 60 years eventually develop Parkinson's disease, but neuropathological findings suggest that ~10% of subjects older than 60 years reach presymptomatic stages of

Parkinson's disease, exhibiting Lewy bodies and signs of neurodegeneration in the SN (Fearnley and Lees, 1991). This agrees with the frequency of marked SN hyperechogenicity in the normal population. Whereas the rate of individuals with SN hyperechogenicity does not change with age in adults (Berg *et al.*, 1999a), elderly patients without prediagnosed extrapyramidal disorder but with SN hyperechogenicity develop more frequent and more severe signs of motor retardation and in some cases even typical Parkinson's disease than those with a regular echogenicity of the SN (Berg *et al.*, 2001c). Moreover, patients with SN hyperechogenicity but without prediagnosed Parkinson's disease developed more often and more severe extrapyramidal symptoms when neuroleptic therapy had to be applied (Berg *et al.*, 2001b). These clinical observations substantiate the functional relevance of SN hyperechogenicity in healthy adults. In several PET and SPECT studies of young healthy subjects, marked SN hyperechogenicity has been associated to a subclinical impairment of the nigrostriatal dopaminergic system (Berg *et al.*, 1999a, 2002; Sommer *et al.*, 2004; Walter *et al.*, 2004b).

In the present study a 3-fold rate of marked SN hyperechogenicity was found in depressed non-parkinsonian patients compared to the normal population. This is in line with the results of epidemiological studies that have estimated a risk of 2.2 to 3.1 for depressed patients for later developing Parkinson's disease compared to non-depressed controls (Nilsson *et al.*, 2001; Schuurman *et al.*, 2002; Leentjens *et al.*, 2003). Few studies of the nigrostriatal dopaminergic system in depressed patients without Parkinson's disease have been reported. Abnormal speech articulation patterns in depressed patients similar to that of Parkinson's disease patients (Flint *et al.*, 1993), increased frequency of motor retardation in patients with major depression (Lemke *et al.*, 1999, 2000), and Parkinson's disease-like decrease of striatal dopamine transporter density in depressed patients on SPECT studies (Neumeister *et al.*, 2001) suggest an impairment of the nigrostriatal dopaminergic system in depression. Findings of a recent functional MRI study in non-parkinsonian patients with major depression imply involvement of dopamine-related neuroanatomical substrates of the ventrolateral prefrontal cortex, the orbitofrontal cortex and the striatum in altered reward processing and anhedonic symptoms (Tremblay *et al.*, 2005). The dopaminergic projections arise from neurons in the ventral mesencephalon near the SN and project to limbic and cortical structures that mediate reward processing and cognition. Whereas little is known on the degree of degeneration of mesencephalic dopaminergic neurons in non-parkinsonian depressed subjects, neuropathological studies in depressed Parkinson's disease patients have shown that there is a greater degeneration of dopaminergic neurons in the ventral mesencephalon than in non-depressed Parkinson's disease patients (Kapur and Mann, 1992). Findings of a recent PET study support the idea that depression in

Parkinson's disease might be associated with a loss of dopamine (and noradrenaline) innervation in the limbic system (Remy *et al.*, 2005). The higher frequency of marked SN hyperechogenicity in depressed compared to non-depressed Parkinson's disease patients, found in the present study, might be a correlate of a more widespread pathology involving mesolimbic dopaminergic neurons in Parkinson's disease patients with depression, even though it has to be considered that SN hyperechogenicity does not reflect the neuronal degeneration itself (Spiegel *et al.*, 2006). Since the pathology underlying SN hyperechogenicity is already present at early adult ages, this might also lead to a liability to depression via altered mesolimbic dopaminergic activity, prior to, or even independently from a possible manifestation of Parkinson's disease later in life. Findings of the present study suggest that TCS of SN might be useful to detect those patients with depressive disorder who are at increased risk of developing Parkinson's disease. To further substantiate the proposed association of depression and the development of Parkinson's disease, functional neuroimaging studies in patients with depression and SN hyperechogenicity but without the clinical picture of Parkinson's disease are warranted.

Brainstem raphe TCS findings agree with previous reports of reduced echogenicity of brainstem raphe as a characteristic finding in MDD and in depression associated with Parkinson's disease, but rarely in healthy adults, bipolar affective disorders, schizophrenia or Parkinson's disease without depression (Becker *et al.*, 1995b, 1997; Berg *et al.*, 1999b; Walter *et al.*, 2007). This TCS finding could be correlated to signal alteration on MRI and was suggested to reflect structural disruption of the brainstem raphe, resulting in impaired serotonergic innervation (Berg *et al.*, 1999b; Becker *et al.*, 2001). In the present study, mean raphe echogenicity scores in depressed patients are higher compared to earlier reported scores which can be attributed to improvements in the ultrasound technology in recent years. Becker and co-workers (1995, 1997) applied an ultrasound system of former generation (Sonoline CF; Siemens, Erlangen, Germany), whereas the ultrasound system used in this study was a present-day machine displaying brain structures with higher sensitivity which made classification of brainstem raphe echogenicity as markedly reduced (i.e. invisible) or moderately reduced (i.e. interrupted) less likely. A similar effect has been previously demonstrated for measurement of SN echogenicity with the respective ultrasound systems (Berg *et al.*, 2001a). Nevertheless, high interrater correlation in this and earlier studies underlines reliability of brainstem raphe TCS.

To further elucidate whether TCS findings are helpful for detection of depressive patients with an increased risk for developing Parkinson's disease, we compared TCS findings in Parkinson's disease patients who had depressive disorder prior to Parkinson's disease onset, and those without or with later onset of depression. It turned out that the combination of the findings of marked SN

hyperechogenicity and reduced raphe echogenicity is characteristic for Parkinson's disease patients with depressive disorder prior to onset of Parkinson's disease, and that, in non-parkinsonian patients with depression, these combined TCS abnormalities are significantly associated with presence of right-to-left asymmetry on the UPDRS. Neither severity, duration or diagnostic category of depression, nor gender or age were found to have an impact on the TCS abnormalities or on the presence of motor asymmetry in non-parkinsonian patients with depression in this study. It is well-known that mild, subclinical motor asymmetry may occur 10–20 years before the diagnosis of Parkinson's disease can be established according to diagnostic criteria (Lees, 1992). Also, depressive and anxiety disorders may occur already 10–20 years before onset of Parkinson's disease (Shiba *et al.*, 2000). As psychomotor retardation is frequent in depressive disorders (Lemke *et al.*, 1999, 2000), a prevalent liability to motor asymmetry might emerge with the depressive state. The underlying mechanism, possibly indicated by sonographic abnormality of brainstem raphe, might be an impaired serotonin-mediated regulation of striatal dopamine transmission (Alex *et al.*, 2005). Interestingly, in Parkinson's disease patients with onset of depression prior to onset of Parkinson's disease, a clear correlation of larger SN echogenic sizes with earlier onset of Parkinson's disease was seen in the present study. A similar high correlation was demonstrated previously in *parkin* mutation carriers who were members of the same kindred (Walter *et al.*, 2004b). It needs to be elucidated in further studies whether, or not, this similarity is due to a predominantly genetic determination of Parkinson's disease in subjects who suffer depression prior to onset of Parkinson's disease as proposed earlier (Santamaria *et al.*, 1986). Findings of the present study suggest that depressed patients with combined TCS abnormality of SN and brainstem raphe are at increased risk of developing Parkinson's disease. This needs to be confirmed in long-term follow-up studies of these patients.

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