Transcranial sonography findings related to depression in parkinsonian disorders: cross-sectional study in 126 patients

Angela E.P. Bouwmans, Wim E.J. Weber, Albert F.G. Leentjens, Werner H. Mess

Background: Transcranial sonography (TCS) has emerged as a potential diagnostic tool for Parkinson's disease. Recent research has suggested that abnormal echogenicity of substantia nigra, raphe nuclei and third ventricle is associated with increased risk of depression among these patients. We sought to reproduce these findings in an ongoing larger study of patients with parkinsonian syndromes.

Methods: 126 patients with parkinsonian symptoms underwent the Hamilton Depression Scale, and TCS of the substantia nigra (SN) (n = 126), the raphe nuclei (RN) (n = 80) and the third ventricle (n = 57). We then calculated correlation between depression and hyper-echogenic SN, hypo-echogenic RN and a wider third ventricle.

Results: In patients with PD we found no significant difference of the SN between non-depressed and depressed patients (46% vs. 22%; p = 0.18). Non-depressed patients with other parkinsonisms more often had hyperechogenicity of the SN than depressed patients (51% vs. 0%; p = 0.01). We found no relation between depression and the echogenicity of the RN or the width of the third ventricle.

Conclusions: In patients with parkinsonian syndromes we found no association between depression and hyper-echogenic SN, hypo-echogenic RN or a wider third ventricle, as determined by transcranial sonography.

Transcranial sonography findings related to depression in parkinsonian disorders: cross-sectional study in 126 patients: cross-sectional study in 126 patients

Angela E.P. Bouwmans MD[1] , Wim E.J. Weber MD PhD[1], Albert F. G. Leentjens MD PhD[2], and Werner H. Mess MD PhD[3]

Departments of [1]Neurology, [2]Psychiatry, and [3]Clinical Neurophysiology, Maastricht University Medical Centre, Maastricht, The Netherlands

Corresponding author: dr. A.E.P Bouwmans, Dept. of Neurology, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands

Tel.: +31-43/3875058

Fax. : +31-43/3877055

E-mail : angelabouwmans@outlook.com

Abstract

Background Transcranial sonography (TCS) has emerged as a potential diagnostic tool for Parkinson's disease. Recent research has suggested that abnormal echogenicity of substantia nigra, raphe nuclei and third ventricle is associated with increased risk of depression among these patients. We sought to reproduce these findings in an ongoing larger study of patients with parkinsonian syndromes of recent onset.

Methods 126 patients with parkinsonian symptoms underwent the Hamilton Depression Scale, and TCS of the substantia nigra (SN) (n = 126), the raphe nuclei (RN) (n = 80) and the third ventricle (n = 57). We then calculated correlation between depression and hyper-echogenic SN, hypo-echogenic RN and a wider third ventricle.

Results In patients with PD we found no significant difference in echogenicity of the SN between non-depressed and depressed patients (46% vs. 22%; p = 0.18). Non-depressed patients with other parkinsonisms more often had hyperechogenicity of the SN than depressed patients (51% vs. 0%; p = 0.01). We found no relation between depression and the echogenicity of the RN or the width of the third ventricle.

Conclusions In patients with recent-onset parkinsonian syndromes we found no association between depression and hyper-echogenic SN, hypo-echogenic RN or a wider third ventricle, as determined by transcranial sonography.

47 **Trial registration**: ITRSCC NCT0036819

Background

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disease with a worldwide prevalence of 41 to 1903 per 100,000 (Pringsheim et al. 2014). Diagnosis, especially in the early stages, is difficult, as there is no definitive diagnostic test. Over the last 10 years transcranial sonography (TCS) of the substantia nigra (SN) has emerged as a promising tool in this regard. Numerous ultrasound studies have found that a significant percentage of patients with IPD have a typical enlarged area of echogenicity in the substantia nigra (SN+), which is thought to be associated with increased iron concentrations (Vlaar et al. 2009).

Although PD is mostly known for its motor symptoms, it has now become clear that non-motor symptoms, such as depression, often contribute to the burden of disease (Reijnders et al. 2008). Depression has a major impact on PD patients: depressed PD patients have worse motor function, more cognitive symptoms, and a lower quality of life (Reijnders et al. 2008; Schrag 2006; Schrag et al. 2010). The pathogenesis of depression in PD is still unknown. Studies have suggested that the serotonergic raphe nuclei (RN) might be involved (Becker et al. 2001; Chagas et al. 2013; Kostic & Filippi 2011; Leentjens 2004; Palhagen et al. 2008).

Sonography researchers have thus investigated the RN in PD patients, and reported that its echogenicity was reduced in depressed PD patients compared to non-depressed PD patients and healthy control subjects (Becker et al. 1997; Berg et al. 1999b; Cho et al. 2011; Stankovic et al. 2015; Zhang et al. 2015). Additionally, SN hyperechogenicity and a wider third ventricle has also been reported to be associated with an increased risk of depression (Krogias et al. 2011;

Walter et al. 2007c; Walter et al. 2010). TCS could be clinically useful, as diagnosing depression in PD patients is difficult (Bouwmans & Weber 2012; Poewe & Luginger 1999; Shulman et al. 2002).

We recently finished a prospective cohort study on the diagnostic accuracy of TCS in early parkinsonian patients (Bouwmans et al. 2013), and we used this dataset to explore the association between depressive symptoms and echogenic features of the SN, RN, and third ventricle in PD patients.

Patients and methods

Design

This study was a cross-sectional study, nested within a prospective cohort study that aimed to test the diagnostic accuracy of TCS of the SN in patients who were referred to a neurologist by their general practitioner (GP) because of recent-onset parkinsonism of unclear origin (Bouwmans et al. 2013) The study protocol was published before patient inclusion started (Vlaar et al. 2007). The main finding of the cohort study was that the diagnostic accuracy of the echogenicity of the SN as a diagnostic test for early PD is not sufficient for routine clinical use. The Institutional Review Board (IRB) of Maastricht University Medical Centre approved the study (MEC 05–228, 4 April 2006), which was registered in the ClinicalTrials.gov database as NCT0036819.

Patients

We considered 283 consecutive patients with parkinsonism of unknown origin, who were referred to the neurology outpatient clinic of Maastricht University Medical Centre, Maastricht and the Orbis Medical Centre, Sittard, the Netherlands (Presently: Zuyderland Medical Centre). Patients who did not consent or those in whom a definite diagnosis could be made at the first visit (n=42) were excluded from the study. Hence, 241 patients were included. Of these, another 69 were excluded: 24 patients who upon examination did not present with clear parkinsonian symptoms or who presented with drug-induced parkinsonism, as well as 45 patients (18.7%) who did not have a sufficient bone window for an adequate TCS examination (See flowchart).

Measures

After signing informed consent, all subjects underwent a structured interview and a neurological examination (Bouwmans et al. 2013; Vlaar et al. 2007). These tests were performed by a physician not treating the patient and blinded for information in clinical records. Depressive symptoms were measured with the observer-rated 17 item Hamilton Depression Rating Scale (HAMD). This scale has a good reliability and validity, both in PD patients as well as in the general population. (Leentjens et al. 2000; Schrag et al. 2007). The score range is 0 to 52, with scores of 11 and higher suggesting clinically relevant depressive symptoms. Motor symptoms were measured with the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Movement Disorder Society Task Force on Rating Scales for Parkinson's 2003).

Within two weeks of inclusion all patients underwent a TCS at the department of Clinical Neurophysiology of one of the two hospitals. In Maastricht University Medical Center, visualization of the RN was included in the TCS protocol from the start of the study. One year later, measurement of the third ventricle was included as well. In the Orbis Medical Center, Sittard, only the SN was visualized.

TCS was performed using a SONOS 5500 system (Philips, Eindhoven, the Netherlands). The examination took place in a darkened room with the patient already lying on the examination table before the investigator entered the room, in order to minimize the risk of identification of a patient’s clinical signs. Patient and investigator were instructed not to discuss symptoms or diagnoses.

TCS was performed bilaterally through the pre-auricular bone window with a 2–4 MHz phased array transducer. The quality of the bone window was scored as good, moderate or inferior. Two different methods were applied for the evaluation of the SN. First, the presence or absence of a clearly visible SN was scored (qualitative method). Second, the SN area was encircled

manually and calculated automatically (quantitative method). This was only performed when the hyperechogenicity was located within the anatomical distribution of the SN, meaning that it showed a typical oblique stripe-shaped configuration. Both the right and left SN were measured from both sides.

The RN were identified if they met the criteria of an anatomic structure equally echo-intense to the red nucleus and localized in the transverse plane of the midbrain with a length extending from anterior to posterior, not interrupted. Echogenicity of the RN was rated using a visual scoring system resulting in a semi-quantitative assessment. We scored the RN as hypo-echogenic (RN-) when this structure had a reduced echogenicity compared to the surrounding brain structures or when the anatomic structure was interrupted. We scored the RN as hyperechogenic (RN+) on the TCS when it showed as an uninterrupted relatively echo-intense structure. The patient was scanned from both sides because of the bone window variability in quality of visualization of the RN from right to left. We used the best possible result, so if the RN was absent on one side, but visible at the other side, it was scored as hyperechogenic.

The transverse diameter of the third ventricle was measured from both sides on a standardized diencephalic examination plane.

Two years after inclusion, patients were re-examined by two movement disorder neurologists to obtain a final clinical diagnosis, using the official diagnostic criteria for the several parkinsonian disorders (Gilman et al. 2008; Hughes et al. 1992; Litvan et al. 1996; Litvan et al. 1999; McKeith et al. 2005), which served as a gold standard for our study. These investigators were blinded for all test results, and none of the neurologists had seen the patient before. They were asked to interview and examine the patient, as they would normally do during a routine neurologic

153 consultation. The neurologists filled in the same standard form as had been done by the including
154 investigator during the first visit of the patient, which included, among others, the Unified
155 Parkinson's Disease Rating Scale (UPDRS)-III score. Afterwards the neurologists received these
156 scores of the patient at the first visit, so that they could evaluate whether the patient had had any
157 progression on that scale. Each neurologist was then asked to reach a final clinical diagnosis of
158 the parkinsonian syndrome. One investigator compared these scores and when there was no
159 agreement, the two neurologists were asked to discuss these patients using their notes, in an
160 effort to reach agreement on the final diagnosis (Bouwmans et al. 2013).
161

Statistics

SPSS 21.0 for Windows was used for the statistical analysis. Comparing categorical variables was done by chi-square test. The two-sample t-test was used for comparing continuous variables. Before performing a post-hoc test, we used the homogeneity of variances to decide which post-hoc test was suitable. When showing a good homogeneity, we chose the Bonferroni or Tamhane T2 test for further analyses, otherwise. P values of < 0.05 were considered significant.

Results

Patient characteristics

We allocated patients who were eventually diagnosed with essential tremor (ET) in the group of parkinsonism, because of the pathophysiologic resemblance with PD (Adler et al. 2011; Fekete & Jankovic 2011; Louis & Ottman 2013; Shahed & Jankovic 2007; Tan et al. 2008). We had an insufficient bone window in 18.7% of our patients. This is in line with earlier studies that report an insufficient bone window in 10 to 20% of participants, or even up to 59% of women over 60 years (Okawa et al. 2007; Walter et al. 2007a).

Eventually, we were able to obtain interpretable TCS images of the SN in 126 patients with HAMD rating scale scores. We did TCS of the RN in only one of the two hospitals, so in the end we had 80 patients with RN TCS images. Only later on in the study did we start measuring the width of the third ventricle (An amendment to the study protocol was made), so this echo feature was available for only 57 of the 126 patients (See flow chart).

At follow-up, 72 (57%) patients were clinically diagnosed with PD. 19 (15%) patients had atypical parkinsonian syndromes (APS), such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia (LBD) and corticobasal degeneration (CBD). Nineteen (15%) patients had vascular parkinsonism (VP) and 16 (13%) were diagnosed with ET (See table 1). The subgroups differed significantly on a number of variables, with PD patients being younger and having higher (worse) UPDRS scores (Table 1). The average HAMD scores did not differ between the groups. Sixteen (13%) of the patients had a HAMD $\geq$ 11, indicating

clinically relevant depressive symptoms. The percentage of patients with a hyperechogenic SN and the percentage with hypo-echogenic RN, did not differ between the group with PD and the one with other parkinsonisms. The width of the third ventricle was also not significantly different between the two groups.

Depression and echo features in PD and other parkinsonisms

Nine (13%) of the 72 patients with PD had a HAMD > 11 versus 7 of the 4 patients with other parkinsonisms. There were no differences in the three TCS features between depressed and non-depressed PD patients. In patients with other parkinsonisms we found a significantly higher frequency of hyperechogenic SN in non-depressed patients (See Table 2). There were no significant differences in echo features of RN and the third ventricle between depressed and non-depressed patients with other parkinsonisms (See figures 1-3).

209 **Discussion**
210

211 In this cross-sectional study of 126 early stage parkinsonian patients we did not find any relation
212 between the presence of depressive symptoms and the echogenicity of the SN, RN nor the width
213 of the third ventricle. We found a higher frequency of hyperechogenicity of the SN in the non-
214 depressed patients with other parkinsonisms, but the significance of this remains unclear as it is
215 the result of a posthoc subgroup analysis.
216

217 The major limitation of our study is that it is a secondary analysis of a study that was not
218 powered to detect differences in echogenicity of the SN and RN, or width of the third ventricle
219 resulting from the severity of depressive symptoms. This resulted in a relatively low proportion
220 of patients with clinically relevant depressive symptoms and subgroup analyses were done with a
221 limited number of depressed patients. Because of that, our results must be seen as exploratory
222 and interpreted with caution. Especially the lack of a significant difference in the proportion of
223 hyperechogenicity of the SN between depressed and non-depressed PD patients may be due to a
224 lack of power. Another limitation is the lack of a formal psychiatric assessment to support a
225 diagnosis of depression based on diagnostic criteria. However, a HAMD score ≥ 11 is considered
226 a good indicator of clinically relevant depressive symptoms and has been used to screen for
227 depression in several studies (Leentjens et al. 2000; Reijnders et al. 2010; Schrag 2011; Schrag
228 et al. 2007).
229

230 As the RN are thought to play a role in the pathogenesis of depression, investigators have used
231 TCS to visualize these structures in depressed patients. They found that depressed (Becker et al.
232 1995; Becker et al. 2001; Becker et al. 1994; Walter et al. 2007c; Walter et al. 2007d) and

bipolar patients (Krogias et al. 2011) have a reduced echogenicity of the RN compared to healthy controls. Others reported that PD patients with depression have lower RN echogenicity compared to non-depressed PD patients and healthy control subjects (Becker et al. 1997; Berg et al. 1999b; Cho et al. 2011; Stankovic et al. 2015; Walter et al. 2007b; Zhang et al. 2015) suggesting that hypo-echogenicity of the RN may be a sign of (preclinical) dysfunction of the limbic system. However, in our study we could not confirm these findings.

There are two essential differences between the above five studies that did find an association and ours that did not. Firstly, patient selection: ours was a prospective, registered, study in which consecutive patients were enrolled. The above studies, with the exception of Stankovic's, did not describe how patients were recruited, which might have biased results (Colditz 2010). Another difference is disease duration of the included patients: with the exception of Cho's study, all included patients with longer disease duration, up to 17 yrs. even (Berg et al. 1999a). This approach is useful in pilot experiments, but when one wants to assess diagnostic accuracy of a technique it is preferable to include patients who have not yet been definitely diagnosed (Bachmann et al. 2009).

Some studies have suggested a relation between the width of the third ventricle and the presence of depression (Krogias et al. 2011), as enlargement of the third ventricle may be a reflection of the atrophy of the surrounding structures (Hendrie & Pickles 2010). We were also not able to confirm these findings.

In a meta-analysis we did on TCS in parkinsonian syndromes we found that in 7 retrospective studies a decreased echo-intensity of the RN was found more often in depressed (46%) than in non-depressed IPD patients (16%). Our present study does not accord with that observation. We hypothesize that one of the main reasons for this is publication bias, where negative studies on TCS tend not to be published. We did not formally test that in our meta-analysis, but another example is our recent negative study on the accuracy of TCS to diagnose IPD. Many studies (Becker et al. 1995b; Berg et al. 2001; Gaenslen et al. 2008; Huang et al. 2007; Kim et al. 2007; Mehnert et al. 2010; Ressner et al. 2007; Spiegel et al. 2006; Walter et al. 2002) found a striking association between a hyperechogenic SN and the diagnosis of PD, but in a carefully designed and executed diagnostic accuracy study we could not confirm these results (Bouwmans et al. 2013).

In conclusion, in early stage parkinsonian patients we did not find any relation between the presence of depressive symptoms and the echogenicity of the SN, RN nor the width of the third ventricle. At present this technique has limited diagnostic value to diagnose or predict depression in parkinsonian patients.

.

278

279

280

281

References:

Bachmann LM, ter Riet G, Weber WE, and Kessels AG. 2009. Multivariable adjustments counteract spectrum and test review bias in accuracy studies. *J Clin Epidemiol* 62:357-361 e352. 10.1016/j.jclinepi.2008.02.007

Becker G, Becker T, Struck M, Lindner A, Burzer K, Retz W, Bogdahn U, and Beckmann H. 1995. Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. *Biol Psychiatry* 38:180-184. 0006-3223(94)00263-3 [pii]
10.1016/0006-3223(94)00263-3

Becker G, Berg D, Lesch KP, and Becker T. 2001. Basal limbic system alteration in major depression: a hypothesis supported by transcranial sonography and MRI findings. *Int J Neuropsychopharmacol* 4:21-31. doi:10.1017/S1461145701002164
S1461145701002164 [pii]

Becker G, Struck M, Bogdahn U, and Becker T. 1994. Echogenicity of the brainstem raphe in patients with major depression. *Psychiatry Res* 55:75-84.

Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, Lindner A, Reichmann H, Riederer P, Beckmann H, and Reiners K. 1997. Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. *J Neurol Neurosurg Psychiatry* 63:590-596.

Berg D, Becker G, Zeiler B, Tucha O, Hofmann E, Preier M, Benz P, Jost W, Reiners K, and Lange KW. 1999a. Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. *Neurology* 53:1026-1031.

Berg D, Supprian T, Hofmann E, Zeiler B, Jager A, Lange KW, Reiners K, Becker T, and Becker G. 1999b. Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. *J Neurol* 246:1186-1193.

Bouwmans AE, Vlaar AM, Mess WH, Kessels A, and Weber WE. 2013. Specificity and sensitivity of transcranial sonography of the substantia nigra in the diagnosis of Parkinson's disease: prospective cohort study in 196 patients. *BMJ Open* 3. bmjopen-2013-002613 [pii]
10.1136/bmjopen-2013-002613

Bouwmans AE, and Weber WE. 2012. Neurologists' diagnostic accuracy of depression and cognitive problems in patients with parkinsonism. *BMC Neurol* 12:37. 1471-2377-12-37 [pii]
10.1186/1471-2377-12-37

Chagas MH, Linares IM, Garcia GJ, Hallak JE, Tumas V, and Crippa JA. 2013. Neuroimaging of depression in Parkinson's disease: a review. *Int Psychogeriatr* 25:1953-1961. S1041610213001427 [pii]
10.1017/S1041610213001427

Cho JW, Baik JS, and Lee MS. 2011. Mesencephalic midline change on transcranial sonography in early Parkinson's disease patients with depression. *J Neurol Sci* 310:50-52. S0022-510X(11)00477-1 [pii]
10.1016/j.jns.2011.07.055

Colditz GA. 2010. Overview of the epidemiology methods and applications: strengths and limitations of observational study designs. *Crit Rev Food Sci Nutr* 50 Suppl 1:10-12. 10.1080/10408398.2010.526838

328 Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW,
329 Colosimo C, Durr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn
330 N, Revesz T, Robertson D, Sandroni P, Seppi K, and Vidailhet M. 2008. Second
331 consensus statement on the diagnosis of multiple system atrophy. *Neurology* 71:670-676.
332 71/9/670 [pii]
333 10.1212/01.wnl.0000324625.00404.15
334 Hendrie CA, and Pickles AR. 2010. Depression as an evolutionary adaptation: anatomical
335 organisation around the third ventricle. *Med Hypotheses* 74:735-740. S0306-
336 9877(09)00705-1 [pii]
337 10.1016/j.mehy.2009.10.026
338 Hughes AJ, Daniel SE, Kilford L, and Lees AJ. 1992. Accuracy of clinical diagnosis of
339 idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol*
340 *Neurosurg Psychiatry* 55:181-184.
341 Kostic VS, and Filippi M. 2011. Neuroanatomical correlates of depression and apathy in
342 Parkinson's disease: magnetic resonance imaging studies. *J Neurol Sci* 310:61-63. S0022-
343 510X(11)00298-X [pii]
344 10.1016/j.jns.2011.05.036
345 Krogias C, Hoffmann K, Eyding J, Scheele D, Norra C, Gold R, Juckel G, and Assion HJ. 2011.
346 Evaluation of basal ganglia, brainstem raphe and ventricles in bipolar disorder by
347 transcranial sonography. *Psychiatry Res* 194:190-197. S0925-4927(11)00122-3 [pii]
348 10.1016/j.pscychresns.2011.04.002
349 Leentjens AF. 2004. Depression in Parkinson's disease: conceptual issues and clinical
350 challenges. *J Geriatr Psychiatry Neurol* 17:120-126. 10.1177/0891988704267456
351 Leentjens AF, Verhey FR, Lousberg R, Spitsbergen H, and Wilmink FW. 2000. The validity of
352 the Hamilton and Montgomery-Asberg depression rating scales as screening and
353 diagnostic tools for depression in Parkinson's disease. *Int J Geriatr Psychiatry* 15:644-
354 649. 10.1002/1099-1166(200007)15:7<644::AID-GPS167>3.0.CO;2-L [pii]
355 Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman
356 J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, and Zee DS. 1996. Clinical
357 research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-
358 Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*
359 47:1-9.
360 Litvan I, Grimes DA, Lang AE, Jankovic J, McKee A, Verny M, Jellinger K, Chaudhuri KR, and
361 Pearce RK. 1999. Clinical features differentiating patients with postmortem confirmed
362 progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 246 Suppl 2:II1-
363 5. 9246S001.415 [pii]
364 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE,
365 Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del
366 Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G,
367 Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka
368 K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina
369 JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, and
370 Yamada M. 2005. Diagnosis and management of dementia with Lewy bodies: third report
371 of the DLB Consortium. *Neurology* 65:1863-1872. 01.wnl.0000187889.17253.b1 [pii]
372 10.1212/01.wnl.0000187889.17253.b1

373 Movement Disorder Society Task Force on Rating Scales for Parkinson's D. 2003. The Unified
374 Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov Disord*
375 18:738-750. 10.1002/mds.10473
376 Okawa M, Miwa H, Kajimoto Y, Hama K, Morita S, Nakanishi I, and Kondo T. 2007.
377 Transcranial sonography of the substantia nigra in Japanese patients with Parkinson's
378 disease or atypical parkinsonism: clinical potential and limitations. *Intern Med* 46:1527-
379 1531. JST.JSTAGE/internalmedicine/46.0271 [pii]
380 Palhagen SE, Carlsson M, Curman E, Walinder J, and Granerus AK. 2008. Depressive illness in
381 Parkinson's disease--indication of a more advanced and widespread neurodegenerative
382 process? *Acta Neurol Scand* 117:295-304. ANE986 [pii]
383 10.1111/j.1600-0404.2007.00986.x
384 Poewe W, and Luginger E. 1999. Depression in Parkinson's disease: impediments to recognition
385 and treatment options. *Neurology* 52:S2-6.
386 Pringsheim T, Jette N, Frolkis A, and Steeves TD. 2014. The prevalence of Parkinson's disease:
387 a systematic review and meta-analysis. *Mov Disord* 29:1583-1590. 10.1002/mds.25945
388 Reijnders JS, Ehrt U, Weber WE, Aarsland D, and Leentjens AF. 2008. A systematic review of
389 prevalence studies of depression in Parkinson's disease. *Mov Disord* 23:183-189; quiz
390 313. 10.1002/mds.21803
391 Reijnders JS, Lousberg R, and Leentjens AF. 2010. Assessment of depression in Parkinson's
392 disease: the contribution of somatic symptoms to the clinimetric performance of the
393 Hamilton and Montgomery-Asberg rating scales. *J Psychosom Res* 68:561-565. S0022-
394 3999(09)00416-4 [pii]
395 10.1016/j.jpsychores.2009.10.006
396 Schrag A. 2006. Quality of life and depression in Parkinson's disease. *J Neurol Sci* 248:151-157.
397 S0022-510X(06)00226-7 [pii]
398 10.1016/j.jns.2006.05.030
399 Schrag A. 2011. Apathy and depression scales in Parkinson's disease: are they good enough? *J*
400 *Neurol Sci* 310:216-219. S0022-510X(11)00307-8 [pii]
401 10.1016/j.jns.2011.05.045
402 Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, Weintraub D,
403 Poewe W, Rascol O, Sampaio C, Stebbins GT, and Goetz CG. 2007. Depression rating
404 scales in Parkinson's disease: critique and recommendations. *Mov Disord* 22:1077-1092.
405 10.1002/mds.21333
406 Schrag A, Sheikh S, Quinn NP, Lees AJ, Selai C, Mathias C, Litvan I, Lang AE, Bower JH,
407 Burn DJ, Low P, and Jahanshahi M. 2010. A comparison of depression, anxiety, and
408 health status in patients with progressive supranuclear palsy and multiple system atrophy.
409 *Mov Disord* 25:1077-1081. 10.1002/mds.22794
410 Shulman LM, Taback RL, Rabinstein AA, and Weiner WJ. 2002. Non-recognition of depression
411 and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* 8:193-
412 197. S1353802001000153 [pii]
413 Stankovic I, Stefanova E, Ziropadja L, Mijajlovic M, Pavlovic A, and Kostic VS. 2015.
414 Transcranial midbrain sonography and depressive symptoms in patients with Parkinson's
415 disease. *J Neurol* 262:689-695. 10.1007/s00415-014-7624-0
416 Vlaar AM, Bouwmans A, Mess WH, Tromp SC, and Weber WE. 2009. Transcranial duplex in
417 the differential diagnosis of parkinsonian syndromes: a systematic review. *J Neurol*
418 256:530-538. 10.1007/s00415-009-0143-8

Vlaar AM, Bouwmans AE, van Kroonenburgh MJ, Mess WH, Tromp SC, Wuisman PG, Kessels AG, Winogrodzka A, and Weber WE. 2007. Protocol of a prospective study on the diagnostic value of transcranial duplex scanning of the substantia nigra in patients with parkinsonian symptoms. *BMC Neurol* 7:28. 1471-2377-7-28 [pii]
10.1186/1471-2377-7-28
Walter U, Behnke S, Eyding J, Niehaus L, Postert T, Seidel G, and Berg D. 2007a. Transcranial brain parenchyma sonography in movement disorders: state of the art. *Ultrasound Med Biol* 33:15-25. S0301-5629(06)01749-2 [pii]
10.1016/j.ultrasmedbio.2006.07.021
Walter U, Dressler D, Wolters A, Wittstock M, and Benecke R. 2007b. Transcranial brain sonography findings in clinical subgroups of idiopathic Parkinson's disease. *Mov Disord* 22:48-54. 10.1002/mds.21197
Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, and Benecke R. 2007c. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. *Brain* 130:1799-1807. awm017 [pii]
10.1093/brain/awm017
Walter U, Prudente-Morrissey L, Herpertz SC, Benecke R, and Hoeppner J. 2007d. Relationship of brainstem raphe echogenicity and clinical findings in depressive states. *Psychiatry Res* 155:67-73. S0925-4927(06)00225-3 [pii]
10.1016/j.pscychresns.2006.12.001
Walter U, Skoloudik D, and Berg D. 2010. Transcranial sonography findings related to non-motor features of Parkinson's disease. *J Neurol Sci* 289:123-127. S0022-510X(09)00783-7 [pii]
10.1016/j.jns.2009.08.027
Zhang YC, Hu H, Luo WF, Sheng YJ, Chen XF, Mao CJ, Xiong KP, Yu LF, Zhang Y, and Liu CF. 2015. Alteration of brainstem raphe measured by transcranial sonography in depression patients with or without Parkinson's disease. *Neurol Sci*. 10.1007/s10072-015-2350-7

Table 1(on next page)

Patient characteristics divided by final diagnoses

PD= Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; DP+= depression present/ having a total score of the HAMD of 11 or more, SN+= hyperechogenic substantia nigra; RN-= hypo-echogenic raphe nuclei [b]

1

	PD (n=72)	Other parkinsonisms (n=54)	P value
Age, years (SD)	68.6 (9.2)	72.2 (9.3)	***0.03***
disease duration ,months (SD)	30.1 (47.1)	41.7 (41.4)	0.15
UPDRS total score,mean (SD)	24.5 (10.6)	10.6 (15.6)	0.06
UPDRS motor score,mean (SD)	13.2 (5.7)	15.0 (7.8)	0.16
HAMD,mean, (SD)	4.6 (5.5**)**	5.8 (5.5)	0.25
DP+ %	12.5	13.0	0.94
SN+ %	43.06	44.4	0.88
RN- %	21.7	17.7	0.65
Third ventricle width,mm	5.4	5.3	0.90

2

3

4

5

6

7

8

9

Table 2(on next page)

Patient characteristics divided by final diagnosis

PD= Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; DP+= depression present/ having a total score of the HAMD of 11 or more, SN+= hyperechogenic substantia nigra; RN-= hypo-echogenic raphe nuclei

1

	PD without depression (n=63)	PD with depression (n=9)	P value	Other parkinsonisms without depression (n=47)	Other parkinsonisms with depression (n=7)	P value
Mean age,years (SD)	69.8 (8.8)	63.9 (10.9)	0.10	71.9 (9.4)	74.3 (9.4)	0.54
Mean duration complaints, months (SD)	32.0 (49.8)	16.4 (14.6)	0.36	44.7 42.7)	21.4 (24.8)	0.17
UPDRS total score, mean (SD)	24.2 (10.3)	26.7 (12.8)	0.82	27.5 (14.3)	42.8 (19.7)	***0.02***
UPDRS motor score,mean (SD)	13.3 (5.4)	12.8 (8.0)	0.82	14.3 (7.5)	20.8 (8.4)	*0.05*
HAMD, mean(SD)	3.0 (3.2)	16.1 (4.4)	***0.00***	4.1 (2.7)	17.0 (6.5)	***0.00***
SN+ %	46.0	22.2	0.18	51.1	0	***0.01***
RN- %	21.1	25.0	0.81	20.0	0	0.32
Third ventricle width,mm (SD)	5.4 (1.9)	5.5 (3.0)	0.84	5.3 (2.5)	5.3 (1.7)	0.95

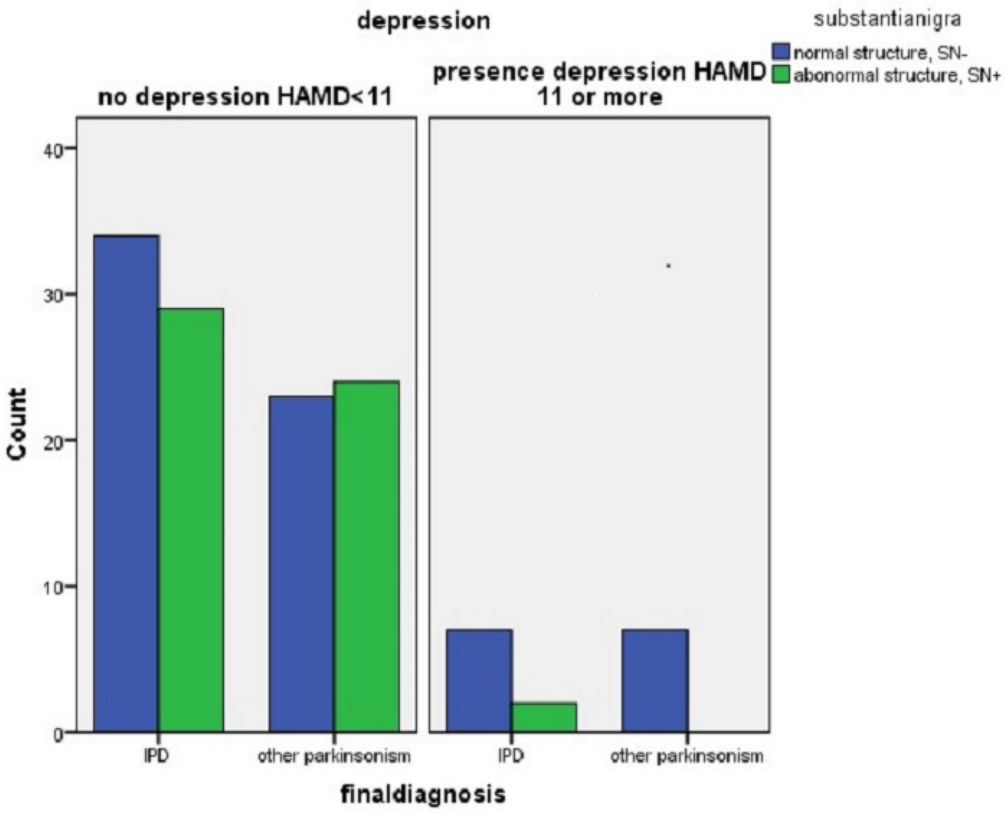
2

3

4
5

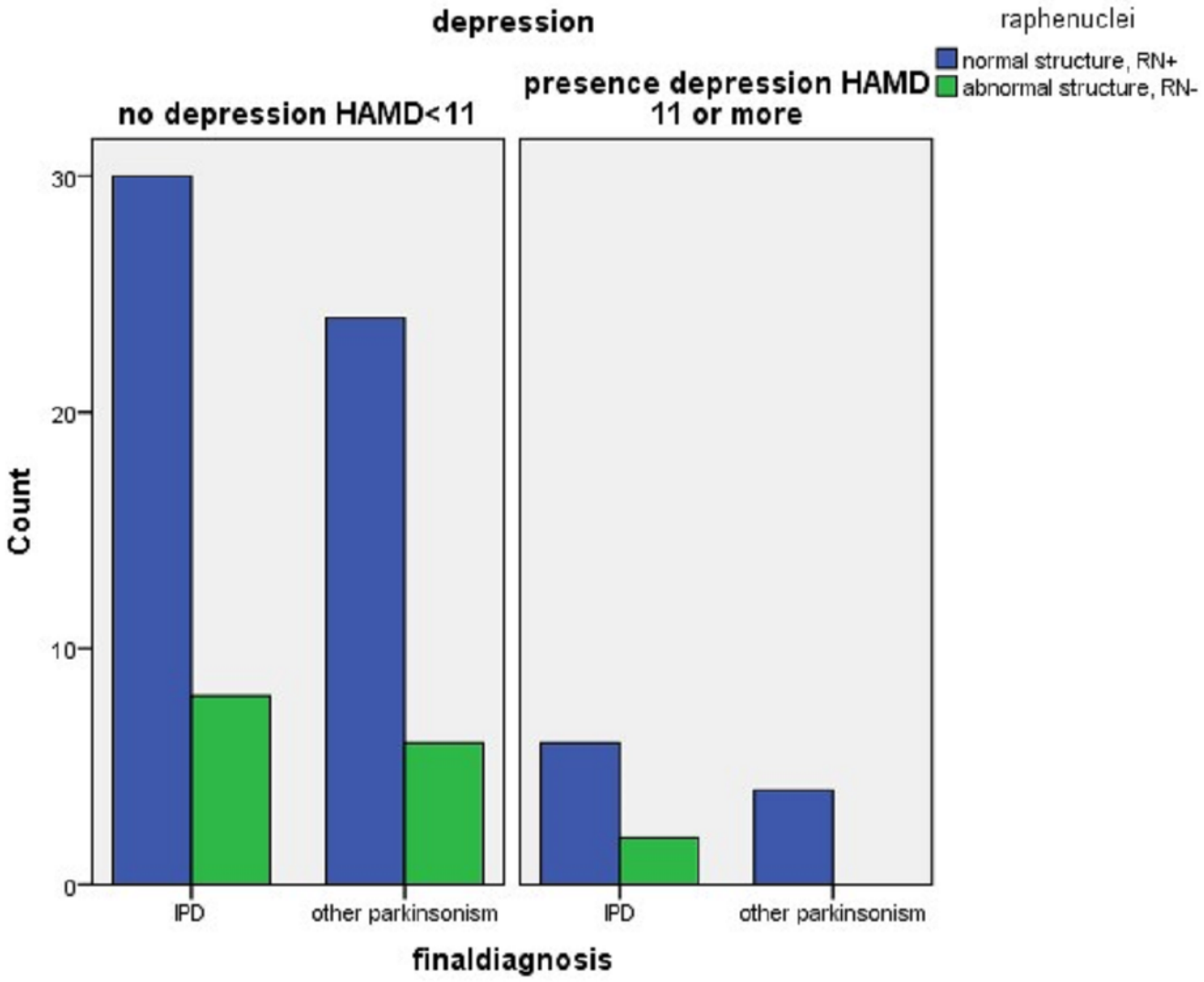
1

Division of echogenicity of the substantia nigra between patients with (n=16) and without a depression (n=110) divided by diagnosis IPD (n=72) and other parkinsonisms (n=54)



2

Division of echogenicity of the raphe nuclei between patients with (n=12) and without a depression (n=68) divided by diagnosis IPD (n=46) and other parkinsonisms (n=34



3

Division of width of third ventricle between patients with (n=10) and without a depression (n=47) divided by diagnosis IPD (n=31) and other parkinsonisms (n=26)