

Diagnosis of dementia – automatic quantification of brain structures

Summary

Background. The aim of the present study was to examine the practical usefulness of fully automatic quantification of brain structures by means of magnetic resonance imaging (MRI) for diagnosing dementia of the Alzheimer's type (DAT).

Material and method. MRI scans of the brains of 122 patients referred to a memory clinic were analysed using Neuroquant software, which quantifies the volume of various brain structures. Clinical diagnoses were made by two doctors without knowledge of the MRI results. We performed receiver operating characteristic (ROC) analyses and calculated the area under the curve (AUC). A value of 1 means that all diseased patients have been diagnosed as such and no patient has been falsely diagnosed as diseased.

Results. The mean age of the patients was 67.2 (SD 10.5 years), 60 % were men, 63 had DAT, 24 had another type of dementia, 25 had mild cognitive impairment (MCI) and ten had subjective cognitive impairment (SCI). In the comparison between DAT patients and patients with SCI or MCI, seven of eleven volumes were significantly larger than AUC 0.5. Positive and negative likelihood ratios were less than 5 and more than 0.2, respectively, for the best threshold values of the volumes. Apart from the cerebellum (AUC 0.67), none of the brain structures was significantly different from AUC 0.5 in patients with other dementia disorders compared with patients with DAT.

Interpretation. MRI scans with Neuroquant analyses cannot be used alone to distinguish between persons with DAT and persons without dementia.

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Dementia has a variety of causes. Alzheimer's type is the most common (1). Many patients with signs of dementia are not evaluated (2); on the other hand, patients are referred to memory clinics for evaluation at an earlier stage in the development of the disease today than ten years ago (3). They are younger, and half of them do not meet the criteria for the dementia syndrome and receive the diagnoses «subjective cognitive impairment» or «mild cognitive impairment». There is no definition of the concept «subjective cognitive impairment». It is used for patients who feel that their cognitive capacity is reduced, but in whom neuropsychological testing has failed to reveal cognitive impairment.

There is no single diagnostic test that can determine the existence of a specific dementia disease. The diagnosis should be made in relation to standardised criteria after a thorough examination that includes the patient's history, cognitive testing, physical examination, diagnostic imaging and in many cases spinal fluid testing to determine tau protein and amyloid beta (4).

A significant increase in new dementia cases is expected in the years ahead, and it is therefore important to develop valid and simple diagnostic procedures. New criteria have also been proposed for diagnosing Alzheimer's disease in an early phase (before

the development of dementia). Biomarkers have a more central place in these criteria than in today's ICD 10 criteria (5).

It has long been known that the neurodegeneration in Alzheimer's disease starts in the entorhinal cortex and rapidly spreads to the medial temporal lobes (6). It was demonstrated in the 1990s that medial temporal lobe atrophy, documented by cerebral computer tomography, was typical of patients with DAT (7–9). This knowledge was difficult to apply in clinical practice because the quality of the equipment of the time varied (10).

The results of studies on the use of magnetic resonance imaging (MRI) (11–13) have reported sensitivity and specificity of 80 % to 90 % to distinguish between patients with DAT and healthy elderly people and between patients with DAT and patients with mild cognitive impairment (14, 15). Visual inspection, linear and volumetric measurement are all used (8, 14, 16).

Visual inspection is a rapid method, but studies show different consistency results among those who use this method (17, 18). Non-automatic (manual) volumetric measurement is time-consuming and for that reason cumbersome to use in clinical practice. Neuroquant is one of several automatic methods that have been developed for use in clinical practice (11–13). Normative data are obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) (19). The total volume of the brain and the volumes of specific areas can be calculated using Neuroquant. Age-adjusted measurements are reported for hippocampus, lateral and inferior lateral ventricles.

The objective of this study was to determine the clinical usefulness of Neuroquant for distinguishing patients with the diagnosis DAT from those without dementia,

Main points

- Automatic quantification of brain structures on the basis of MRI scans with Neuroquant best distinguished patients with mild cognitive impairment/no impairment from patients with DAT
- We found that the Neuroquant method did not satisfactorily distinguish patients with DAT from those with other types of dementia

Table 1 Characteristics of 122 patients assessed at the Memory Clinic at Oslo University Hospital. Mean (standard deviation) values unless otherwise specified. MMSE = Mini mental status evaluation, CERAD = Consortium to establish a registry of Alzheimer's disease

Age (years)	67.2 (10.5)
Women, number (%)	49 (40.3)
MMSE score (maximum is 30)	25.1 (4.3)
Clock test score (maximum is 5)	4.0 (3.2)
CERAD ten-word test, learning (maximum is 30)	14.1 (6.1)
CERAD ten-word test, memory (maximum is 10)	3.3 (1.5)

and whether the method can be used to distinguish DAT from other types of dementia.

Material and method

The patients

This is a prospective study of 122 patients with competence to consent referred from primary care doctors to the Memory Clinic at Oslo University Hospital, Ullevål, for dementia evaluation. MRI scans form part of standard examination procedure. The material was collected from patients who were referred between September 2010 and June 2011. A total of 264 patients were referred during this period.

The selection of patients for this project was dependent on the availability for examination with the 3 tesla MRI scanner at Oslo University Hospital. If the doctor providing treatment at the memory clinic saw that the waiting period would be too long, the patients were referred for another MRI scan ($n = 142$). There were no criteria for defining a long waiting period. All the 122 who were asked gave their consent.

The examinations

According to the guidelines for validity studies, all the patients were examined in the same standardised manner. The results of the Neuroquant analysis were not available to the doctors who set the clinical diagnoses (20). The examinations consisted of an interview with patient and family, testing of cognitive function, physical examination, blood sample analyses, MRI scan, single-photon emission computed tomography in cases of suspected Parkinson-plus syndromes or frontotemporal dementia and spinal fluid testing of patients with vague symptoms (3, 4).

In order to illustrate the degree of cognitive impairment in patients, we show the results of some of the cognitive tests that were carried out. The mini-mental status evaluation (MMSE) gives scores between 0 and 30. The lower the score, the greater the cognitive impairment (21, 22). The clock drawing test is scored from 0 to 5. The lower the score, the greater the cognitive impairment (23). The ten-word test investigates learning ability and recall function (anterograde memory). The learning part is scored from 0 to 30. The lower the score, the greater

the cognitive impairment. Recall is scored between 0 and 10, with 0 as the poorest result (24).

Diagnosis

A neurologist (AB) and a psychiatrist (KE), both with more than 20 years of experience in dementia diagnostic work-up, were not present during the consultation, but evaluated all available information for each patient, including the ordinary MRI descriptions but not the Neuroquant analyses. The diagnoses DAT, vascular dementia and Parkinson's dementia were applied according to the ICD 10 criteria. We used the Manchester-Lund criteria to diagnose frontotemporal dementia, and the revised consensus criteria for dementia with Lewy bodies (25, 26).

In accordance with ICD 10, the diagnosis 'Unspecified dementia' was used for patients with dementia that did not satisfy any of the criteria or in patients with mixed conditions. Winblad's criteria were used for mild cognitive impairment, and subjective cognitive impairment was used for patients who experienced memory problems that did not satisfy the criteria for mild cognitive impairment (27). The two doctors disagreed on the diagnosis of eight patients (6.5%). In these cases they reached a consensus diagnosis by discussion.

Magnetic resonance imaging, scanning and analysis

Magnetic resonance imaging was carried out on a 3 tesla MRI scanner (General Electric, Sigma HDx, Milwaukee, Wisconsin, USA). T1-weighted 3D scanning was carried out with IRSPGR pulse sequences with the following variables: inversion time was produced with the aid of sagittal scanning with repetition time (TR) = 7.7 ms, echo time (TE) = ms, field of view = 256 mm, flip angle = 12, section thickness = 1.2 mm, voxel size = 1.2 × 1.0 × 1.3 mm, number of sections = 170, base resolution = 256.

The volume of brain structures was analysed with Neuroquant (CorTechs Labs Inc., San Diego, CA, USA), which performs an automatic segmentation and measures the volume of brain structures (11). In this study we report volumes for anterior cortex, cortical grey matter, cerebellum, hippocampus, amygdala, pallidum, putamen, caudatus,

thalamus, lateral ventricles and inferior lateral ventricles. For each structure we have reported the ratio between brain structure (right + left)/intracranial volume expressed as a percentage, in the article called «volumetric measurements». Neuroquant also reports age-adjusted percentiles for hippocampus, lateral ventricles and inferior lateral ventricles.

Statistics

Data were stored and analysed in SPSS, version 18. Continuous data were almost normally distributed and were subjected to parametric analysis. Simple table analyses were performed and the t-test used to test differences in average volumetric measurements. In accordance with the objective, and because we had few patients with some dementia diseases, we combined the patients into three groups: no dementia (subjective cognitive impairment + mild cognitive impairment) – $n = 35$, DAT – $n = 63$, other dementia diseases – $n = 24$.

To demonstrate the diagnostic strength of the volumetric measurements, we performed receiver operating characteristic (ROC) analyses and specified the area under the curve (AUC) and threshold values for the volumetric measurements that classified most patients correctly. ROC analysis is a method that can be used to provide a measure of the discriminatory power of a diagnostic test. In other words, it shows the relationship between true positive and false positive rates. The area under the curve was calculated to compare the diagnostic discriminatory power of the different brain sizes. Value 1 means that all sick subjects are diagnosed as diseased and none as falsely diseased; 0.5 means that half are correctly classified, i.e. the same result is achieved by chance.

Sensitivity, specificity, positive and negative likelihood ratio were calculated for the best threshold value. A positive likelihood ratio indicates the relationship between true test-positive and false test-positive persons, while a negative likelihood ratio indicates the relationship between false test-negative and true test-negative persons. The two measures are independent of the prevalence of the disease: positive likelihood ratio = sensitivity/1 – specificity, negative likelihood ratio = 1 – sensitivity/specificity. A good diagnostic test should have a positive likelihood ratio of over 5 and a negative likelihood ratio of above 0.2 (28).

Ethics

All patients who are examined at the Memory Clinic are asked whether the results of the examination can be stored in a research register. Over 99% of those with competence to consent agree to this. All those included have competence to consent and signed the consent form. The register is approved by the Norwegian Data Inspectorate, the Regional Committee of Medical

Table 2 Volume of brain structures bilaterally in relation to intracranial volume expressed in per cent for patients without dementia, patients with dementia Alzheimer's type and patients with other types of dementia. Volumetric measurements are expressed as percentages (standard deviation). We did not have measurements of amygdala, caudatus, putamen, pallidum, thalamus, cortical grey matter, anterior cortex and cerebellum for 20 patients.

	No dementia (n = 35)	DAT (n = 63)	Other dementia (n = 24)	P value, t-test ¹	P value, t-test ²
Hippocampus	0.52 (0.06)	0.44 (0.06)	0.47 (0.06)	< 0.001	0.098
Amygdala	0.23 (0.03)	0.19 (0.03)	0.20 (0.05)	< 0.001	0.448
Caudatus	0.50 (0.09)	0.53 (0.08)	0.51 (0.08)	0.087	0.316
Putamen	0.61 (0.07)	0.57 (0.08)	0.52 (1.00)	0.013	0.075
Pallidum	0.12 (0.02)	0.10 (0.03)	0.11 (0.03)	0.051	0.153
Thalamus	1.1 (0.08)	1.1 (0.10)	1.0 (0.16)	0.715	0.573
Anterior cortex	61.5 (2.80)	58.9 (2.90)	58.9 (4.30)	< 0.001	0.971
Cortical grey matter	30.2 (2.10)	28.6 (2.20)	28.4 (3.00)	0.002	0.826
Cerebellum	8.8 (0.74)	8.6 (0.68)	8.1 (0.70)	0.185	0.027
Lateral ventricles	2.24 (1.15)	3.34 (1.44)	4.0 (2.10)	< 0.001	0.195
Inferior lateral ventricles	0.16 (0.07)	0.26 (0.10)	0.24 (0.11)	< 0.001	0.482

¹ No dementia versus DAT

² DAT versus other dementia

Research Ethics of the South-East Norway Regional Health Authority (REC South-East) and the Data Protection Officer at Oslo University Hospital. Clinical data in the study are retrieved from the register, and have been approved by REC South-East.

Results

Patient characteristics are shown in Table 1. The 122 patients had the following diagnoses: subjective cognitive impairment (n = 10), mild cognitive impairment (n = 25), DAT (n = 63), vascular dementia (n = 1), dementia with Lewy bodies or Parkinson's dementia (n = 9), frontotemporal dementia (n = 8) and unspecified dementia (n = 6).

Table 2 shows volumetric measurements for the patients in the three patient groups no dementia, DAT, other types of dementia. We had complete data for all patients for volumetric measurements of hippocampus, lateral ventricles and inferior lateral ventricles. We also had data for the other measurements from 102 patients, 53 of whom had DAT.

In the comparison between patients with DAT and patients with subjective cognitive impairment or mild cognitive impairment, the volumetric measurements for anterior cortex, cortical grey matter, hippocampus, amygdala, putamen, lateral ventricles and inferior lateral ventricles were significantly different from AUC 0.5 (Table 3). In the comparison between DAT and other types of dementia, the cerebellum was the only volumetric measurement that was statistically significantly different from AUC 0.5, with AUC = 0.67 (95% confidence interval (CI) 0.5–0.81), $p = 0.02$. The best threshold value for this volumetric measurement was 8.3%, with sensitivity 72%, specificity 60%, positive likelihood ratio = 1.8 and negative likelihood ratio = 0.63.

In ROC analyses of patients with DAT

versus patients with subjective cognitive impairment or mild cognitive impairment, the three structures with age-corrected percentiles were statistically significantly different from 0.5: hippocampus – AUC 0.80 (95% CI 0.71–0.89), sensitivity 74% and specificity 70% for the 30 percentile (best), lateral ventricles – AUC 0.73 (95% CI 0.63–0.84), sensitivity 73% and specificity 69% for the 80 percentile (best). The results for the inferior lateral ventricles were AUC 0.76 (95% CI 0.66–0.85), sensitivity 71% and specificity 75% for the 75 percentile (best). In ROC analyses of DAT versus other types of dementia, AUC was not significantly different from 0.5 for any of the age-corrected percentiles.

Discussion

We found that the Neuroquant method distinguished patients with DAT from those without dementia who were assessed at a memory clinic. The method did not distinguish between patients with DAT and patients with other types of dementia. The diagnostic power is evaluated as of medium strength for distinguishing between patients with DAT and patients without dementia because the likelihood ratio for the best volumetric measurements was between 2 and 5 and the negative likelihood ratio was between 0.2 and 0.5.

Although the measurements for putamen and cortical grey matter were significantly different from AUC 0.5 in the comparison between patients with DAT and those without dementia (Table 3), this difference does not influence the diagnosis to any particular degree because the positive likelihood ratio was < 2. The same applies to the cerebellum, which was significantly different from AUC 0.5 in the comparison between patients with other forms of dementia and patients with

DAT. We had expected the results of the ROC analyses of the age-standardised percentiles to be better than for structural volume (right + left)/intracranial volume of hippocampus, amygdala and lateral ventricles. They were not, and this may imply that these norms are not well enough validated and that they must be used with caution in clinical practice.

Our results are difficult to compare with earlier Neuroquant studies since positive and negative likelihood ratios are not reported in the latter (11–13, 15). The results are consistent with the results of studies where manual volumetric methods were employed and indicate that Neuroquant analyses are as good as far more time-consuming volumetric measurements (29, 30).

Better results than ours have been reported for some studies in which manual volumetric measurement was used. These are studies in which a comparison has been made between patients with DAT and healthy control subjects (31, 32). We would argue that the results of these studies are less relevant than ours, because a comparison between a diseased patient group and a healthy control group does not reflect the situation in clinical everyday life. In our study, none of the participants were healthy controls; they were all referred by their primary care doctor on suspicion of dementia.

About 50% of those with mild cognitive impairment and 10–20% of those with subjective cognitive impairment will develop dementia in the course of a five-year period (33, 34). Brain changes typical of Alzheimer's disease start 10–15 years before the onset of clinical symptoms. This may mean that a number of our patients with mild cognitive impairment and subjective cognitive impairment have an early stage of Alzheimer's disease even though they do not fulfil

Table 3 Neuroquant's ability to distinguish between patients with dementia Alzheimer's type from patients without dementia. For measurements of the volume of hippocampus, lateral ventricles and inferior lateral ventricles, 98 patients were included in the analyses, 63 of them with DAT. For measurements of the other volumes, 78 patients were included, 53 of them with DAT. The threshold value for volumetric measurements is not reported where AUC was not significantly different from 0.5 in the ROC analysis.

Brain structure	DAT versus no dementia			Best threshold value volume/intracranial volume				
	Area under the curve	95 % CI	P- value	Threshold value (%)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Hippocampus	0.80	0.71–0.90	< 0.001	0.48	74	71	2.6	0.37
Amygdala	0.79	0.69–0.90	< 0.001	0.21	77	70	2.6	0.33
Caudatus	0.38	0.25–0.51	0.084	–	–	–	–	–
Putamen	0.65	0.53–0.78	0.022	0.56	76	49	1.5	0.47
Pallidum	0.63	0.51–0.76	0.051	–	–	–	–	–
Thalamus	0.57	0.44–0.69	0.343	–	–	–	–	–
Anterior cortex	0.77	0.66–0.88	< 0.001	60.72	79	75	3.2	0.28
Cortical grey matter	0.69	0.58–0.81	0.004	28.60	72	52	1.5	0.58
Cerebellum	0.60	0.47–0.73	0.136	–	–	–	–	–
Lateral ventricles	0.76	0.66–0.87	< 0.001	2.56	73	71	2.3	0.38
Inferior lateral ventricles	0.78	0.68–0.87	< 0.001	0.18	73	74	2.7	0.36

the criteria for dementia. This could be one explanation for the relatively low specificity we found for the brain structures (Table 3). Some of the patients in the group without dementia may be in the process of developing DAT and for that reason have atrophy of the hippocampus and amygdala and expanded lateral ventricles. It is more difficult to explain why a number of patients with the diagnosis DAT do not have typical MRI findings for this disease. One reason may be misdiagnosis. Nonetheless, surveys show that the consistency between a neuropathological diagnosis of Alzheimer's disease and the clinicians' diagnosis – DAT – is good, with a sensitivity approaching 90 % and a somewhat lower specificity (35).

The doctors who diagnosed the patients in this study are experienced, which should mean that misdiagnosis is not the primary cause of low sensitivity. A more probable explanation is that Alzheimer's disease does not always start in the entorhinal cortex, but in posterior cortical regions. Volumetric measurements in patients with this atypical development will not be affected in the same manner as they are in patients where the disease starts in the entorhinal cortex.

Our other main finding was that the Neuroquant analyses did not distinguish patients with DAT from those with other dementia diseases. This is not unexpected. According to neuropathological investigations, many patients with clinical dementia symptoms have a mixture of different types of dementia (36). Approximately 75 % of those with the diagnosis neuropathological dementia with Lewy bodies also have neuropathological changes in the brain that indicate concomitant Alzheimer's disease (37). The combination of vascular dementia, dementia with Lewy bodies and DAT is not uncommon either (36). It is possible that automatic

MRI analysis would succeed in distinguishing DAT from frontotemporal dementia, but the group with frontotemporal dementia is too small to test this hypothesis. We have no answer to the question of why the cerebellum was significantly more atrophied in the group with other dementia diseases than in the group with DAT. This may be a random finding.

The study has weaknesses. We have used clinical diagnoses as the gold standard. This may introduce error, because a clinical diagnosis is never 100 % consistent with neuropathological diagnoses. On the other hand, neuropathological diagnoses are not a gold standard either (38). It can be argued that the clinical diagnostics would have been better if dementia markers had been measured in the spinal fluid of all the patients. But spinal fluid biomarkers are not a failproof means of identifying DAT either, or other dementia disorders. Many patients with normal values for tau protein and/or beta-amyloid have symptoms and disease progression consistent with DAT (4).

Another weakness is the inclusion of few patients with mild cognitive impairment and other types of dementia than DAT. In order to obtain definite answers to whether Neuroquant can be used in the differential diagnostic, far more patients with mild cognitive impairment, subjective cognitive impairment and different dementia diseases should be included in a similar study.

The strength of the study is the research design. Patients with competence to consent who were referred for dementia assessment were included continuously, a standard examination procedure was used for them all, and the results of the MRI quantification were not available to the doctors who set the diagnoses. Since more than half of the patients referred to the memory clinic in the

period while the study was in progress were not included, it may be argued that the patients included were subject to a selection process. But this was not systematic selection; it depended only on whether the doctor providing treatment thought that the waiting time for the Neuroquant examination was too long.

Conclusion

Our conclusion is that automatic quantification of brain structures cannot be used as a stand-alone means of examination in dementia assessment, but it can provide support for the results of other clinical investigations. It is important to use methods with a high cost-benefit value in this work, as a strong increase in the number wanting assessment for a possible dementia disorder is expected in the years ahead.

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References

- Engedal K. Diagnostikk og behandling av demens. *Tidsskr Nor Lægeforen* 2002; 122: 520–4.
- Lystrup LS, Lillesveen B, Nygård AM et al. Omsorgstilbud til hjemmeboende personer med demens. *Tidsskr Nor Lægeforen* 2006; 126: 1917–20.
- Brækhus A, Ulstein I, Wyller TB et al. Hukommelsesklinikk – poliklinisk utredning ved mistanke om demenssykdom. *Tidsskr Nor Lægeforen* 2011; 131: 2254–7.
- Brækhus A. Biomarkører ved demens. *Tidsskr Nor Lægeforen* 2011; 131: 2218.
- Dubois B, Feldman HH, Jacova C et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; 6: 734–46.
- Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. *Acta Neurol Scand Suppl* 1996; 165: 3–12.
- Jack CR Jr., Petersen RC, Xu YC et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997; 49: 786–94.
- Scheltens P, Leys D, Barkhof F et al. Atrophy of medial temporal lobes on MRI in «probable» Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992; 55: 967–72.
- Jobst KA, Smith AD, Barker CS et al. Association of atrophy of the medial temporal lobe with reduced blood flow in the posterior parietotemporal cortex in patients with a clinical and pathological diagnosis of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1992; 55: 190–4.
- Oksengaard AR, Haakonsen M, Dullerud R et al. Accuracy of CT scan measurements of the medial temporal lobe in routine dementia diagnostics. *Int J Geriatr Psychiatry* 2003; 18: 308–12.
- Brewer JB, Magda S, Airriess C et al. Fully-automated quantification of regional brain volumes for improved detection of focal atrophy in Alzheimer disease. *AJNR Am J Neuroradiol* 2009; 30: 578–80.
- McEvoy LK, Fennema-Notestine C, Roddey JC et al. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. *Radiology* 2009; 251: 195–205.
- Brewer JB. Fully-automated volumetric MRI with normative ranges: translation to clinical practice. *Behav Neurol* 2009; 21: 21–8.
- Wahlund LO, Almkvist O, Blennow K et al. Evidence-based evaluation of magnetic resonance imaging as a diagnostic tool in dementia workup. *Top Magn Reson Imaging* 2005; 16: 427–37.
- Klöppel S, Stonnington CM, Chu C et al. Automatic classification of MR scans in Alzheimer's disease. *Brain* 2008; 131: 681–9.
- Wahlund LO, Julin P, Lindqvist J et al. Visual assessment of medial temporal lobe atrophy in demented and healthy control subjects: correlation with volumetry. *Psychiatry Res* 1999; 90: 193–9.
- Wattjes MP, Henneman WJ, van der Flier WM et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. *Radiology* 2009; 253: 174–83.
- Galluzzi S, Talassi E, Belussi M et al. Multi-center comparison of medial temporal atrophy in patients with Alzheimer's disease—data from the ICTUS study. *Dement Geriatr Cogn Disord* 2008; 26: 314–22.
- Mueller SG, Weiner MW, Thal LJ et al. The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am* 2005; 15: 869–77, xi–xii, xi–xii.
- Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1994; 271: 389–91.
- Folstein MF, Folstein SE, McHugh PR. «Mental state». A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Engedal K, Haugen P, Gilje K et al. Efficacy of short mental tests in the detection of mental impairment in old age. *Compr Gerontol A* 1988; 2: 87–93.
- Shulman KI. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry* 2000; 15: 548–61.
- Fillenbaum GG, van Belle G, Morris JC et al. Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers Dement* 2008; 4: 96–109.
- McKeith IG, Dickson DW, Lowe J et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; 65: 1863–72.
- Neary D, Snowden JS, Gustafson L et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51: 1546–54.
- Winblad B, Palmer K, Kivipelto M et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; 256: 240–6.
- Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994; 271: 703–7.
- Xu Y, Jack CR Jr, O'Brien PC et al. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. *Neurology* 2000; 54: 1760–7.
- Kantarci K, Xu Y, Shiung MM et al. Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2002; 14: 198–207.
- Bottino CM, Castro CC, Gomes RL et al. Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. *Int Psychogeriatr* 2002; 14: 59–72.
- Pennanen C, Kivipelto M, Tuomainen S et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging* 2004; 25: 303–10.
- Andersson C, Lindau M, Almkvist O et al. Identifying patients at high and low risk of cognitive decline using Rey Auditory Verbal Learning Test among middle-aged memory clinic outpatients. *Dement Geriatr Cogn Disord* 2002; 21: 251–9.
- Almkvist O, Tallberg JM. Cognitive decline from estimated premorbid status predicts neurodegeneration in Alzheimer's disease. *Neuropsychology* 2009; 23: 117–24.
- Mayeux R, Saunders AM, Shea S et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. *N Engl J Med* 1998; 338: 506–11.
- Ince PG, McArthur FK, Bjertness E et al. Neuropathological diagnoses in elderly patients in Oslo: Alzheimer's disease, Lewy body disease, vascular lesions. *Dementia* 1995; 6: 162–8.
- Merdes AR, Hansen LA, Jeste DV et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. *Neurology* 2003; 60: 1586–90.
- Galasko D, Hansen LA, Katzman R et al. Clinical-neuropathological correlations in Alzheimer's disease and related dementias. *Arch Neurol* 1994; 51: 888–95.

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