The diagnostic value of the TNI-93: a memory test suitable for both literate and illiterate patients.

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Research Article

Keywords: TNI-93, memory test, Alzheimer disease, literacy

Posted Date: March 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-274305/v1

Abstract

Background: A significant proportion of Alzheimer disease (AD) patients are illiterate or poorly educated, and only a few memory tests are adapted for these patients. The TNI-93 is a quick memory test that was designed for all patients regardless of their education level. In the present study we aimed at assessing the diagnostic value of the TNI-93 for the screening and diagnosis of patients with biologically confirmed amyloid status.

Method: We included all patients who had a lumbar puncture (LP) for the analysis of AD cerebrospinal fluid (CSF) biomarkers, a full neuropsychological assessment that included the TNI-93 and an anatomical brain imaging (MRI/CT scan) at Avicenne Hospital between January 2009 and November 2019. We compared the TNI-93 scores in A+ patients (patients with amyloid abnormalities) and A- patients according to the A T (N) criteria (NIA-AA 2018). We also compared A+T+ patients to A-T- patients.

Results: 108 patients were included with a mean age of 66.9 ± 8.5 years old, and mean education level of 8.9 ± 5.16 years, illiterate patients represented 27% of the population. Patients from the A+ group (N= 80) were significantly more impaired than patients from the A- group (N=28) on immediate recall (A+: 5.9±2.8; A-: 7.4±2.6; p=0.001), free recall (A+: 3.5±2.7; A-: 5.9±2.8; p< 0.001), total recall (A+: 5.7±3.5; A-: 7.8±2.8; p< 0.001) and on number of intrusions during the recall phase (A+: 1±1.8; A-: 0.1±0.3; p=0.002). Similar results were observed in the memory subgroup but not in patients with presentation other than memory complaint (ie language impairment or others presentation such as behavioural and hallucination). Similar results with increased significance were observed when we compared A+T+ patients (N=50) to A-T- patients (N=26). Analyses of the ROC curves revealed that the best scores of the TNI-93 test to discriminate A+ patients from A- were immediate recall (Area under curve (AUC): 0.70), free recall (AUC: 0.74) and total recall (AUC: 0.74).

Conclusion: We found that the TNI-93's immediate recall, free and total recall are valuable for the diagnosis of amyloid pathology suggestive of AD.

Background:

Alzheimer's disease (AD) affects more than one million patients in France and 35 million worldwide [1]. The diagnosis of AD relies on the association of clinical and biological arguments [2, 3]. Clinically, progressive episodic memory impairment, described as a hippocampal syndrome is considered as the usual presentation of AD [4, 5]. The patient typically shows a recall deficit that is not improved by cueing [6, 7].

A significant proportion of AD patients are illiterate or poorly educated. Illiteracy is defined as the non-acquisition of sufficient mastery of reading, writing, numeracy and basic skills to be autonomous in simple everyday life situations (UNESCO, 2008)[8]. In France, as in other western countries, one third of the population aged above 65 years old is illiterate [9, 10]. In illiterate patients, the hippocampal syndrome

cannot be searched for without memory tests adapted for this specific patient population, and only few adapted clinical tests are available.

Visual memory tests such as the DMS 48 test may be used in illiterate patients, but they are too long for routine clinical practice, and clinicians do not always know them. The TNI-93 [11, 12] developed at Avicenne hospital is a quick and easy test, based on 9 images with an encoding step followed by a delayed free and cued recall. The TNI-93 does not correlate with the level of education and had good sensitivity and specificity for the diagnosis of dementia [11, 12].

AD diagnosis can also be supported by objective and specific biomarkers, such as amyloid PET or cerebrospinal fluid (CSF) analyses of beta amyloid peptide (Aβ42), total Tau and phosphorylated Tau [13]. Hippocampal volume on cerebral MRI [6] and cerebral metabolism on FDG PET scans [7] are altered in AD but these biomarkers are less specific of AD. Based on biomarkers, diagnostic and research criteria have been developed by two main research groups, the International Working Group [2] and the National Institute on Aging Alzheimer's association (NIA-AA)[14]. Following these criteria, CSF analysis is often proposed in the diagnosis process of cognitive disorders notably when the neuropsychological assessment is difficult to interpret. However, CSF analysis is not always possible because the test is not always available, because it sometimes costs too much for the patient, or because there is a medical contraindication to lumbar puncture (LP). It is therefore helpful to know whether there is a correlation between the cognitive presentation and the CSF status, especially in population that are difficult to evaluate and have less access to CSF analysis, such as illiterate patients. The aim of the present study was to examine the diagnostic value of the TNI-93 for the screening and diagnosis of biologically confirmed amyloid status inpatients. Additionally, we aimed to assess the sensitivity and specificity of the test in the global population of patients with cognitive complaint and in subgroups of patients according to the nature of the cognitive complaint (memory, language, or other complaint).

Methods:

Patient: Patient’s data was retrospectively collected from all patients who consulted at the memory clinic of the Avicenne hospital (Bobigny) from January 2009 to November 2019 and underwent a LP. We included all patients who had a LP for the analysis of AD CSF biomarkers, a full neuropsychological assessment that included the TNI-93 test before or at the time of the LP (No later than one year after the LP) and an anatomical brain imaging (MRI or CT scan). Patients with an abrupt onset of cognitive disorders or a Mini-Mental State examination (MMSE) score < 5 (out of 30) were excluded. The confirmation of AD diagnosis relied on the study of the CSF, based on the latest published diagnostic criteria (classification ATN, 2018)[14].

Diagnostic criteria: We used the A T (N) criteria developed by the NIA-AA in 2018 [14] to classify patients in one of the following groups: i). Patients with amyloid abnormalities secondary to a continuum of AD (A+) and ii). Patients with no amyloid abnormalities secondary to a continuum of AD (A-). Then, for

subgroup analyses, we classified patients in one of the following groups: 1. patients with AD (A + T+) and 2. patients with no AD (A-T-).

CSF was collected by a LP sampled in a polypropylene tube, frozen and sent to a storage container in the laboratory of the Lariboisière-Fernand Widal Hospital. The liquid was analyzed and peptide Aβ42 and Aβ40 as well as phosphorylated Tau and total Tau ratio were measured by Innotest® ELISA method (Fujirebio) and then by the technology electrochemiluminescence Elecsys® (Roche) after 2014. Between 2009 and 2019, techniques have changed as well as the interpretation thresholds (supplementary material 1).

Neuropsychological assessment: All patients had a neuropsychological assessment that was carried out by a certified neuropsychologist. Interviews took place with the patient alone or sometimes with a family member for translation needs. All patients underwent the TN-93, and the MMSE. The rest of the neuropsychological assessment included assessment of language, executive functions and memory with tests that varied according to patient's complaint, clinical severity and level of education. The neuropsychological assessment's objective was to draw up a cognitive profile in order to orient the diagnosis.

After the clinical evaluation and complementary exams, patients' diagnosis was discussed and established in a weekly meeting of neurologists, neuropsychologists and radiologists.

TNI-93: The TNI-93 was derived from the MIS (memory impairment screen) [15]. It consists of an A4 sheet with nine black and white drawings (Fig. 1). The instructions are very simple and the test lasts 5 to 10 minutes. There are two stages, encoding and then recall. During the encoding stage, an A4 sheet with nine black and white drawings is placed in front of the patient. Participants first complete a naming task according to the semantic category given by the examiner by answering to the following question: "which one is an …". The semantic categories are as follows: animal, transportation, musical instrument, vegetable, part of the face, furniture, fruit, "something which is used to dress", kitchen utensil. If the patient does not understand the name of the category, the examiner may repeat it with a simpler description (for instance asking to show "an item used for eating" rather than "a kitchen utensil"). After having hidden the images, a cued recall (CR) is immediately undertaken by giving the semantic category as a cue (the same cue previously used). If not all items are returned during the immediate CR, the images are placed in front of the patient a second time with the same encoding procedure as before (a third time is possible). After a 20-second interfering test, a 2-minute free recall test is performed (score ranging from 0 to 9, pathological < 6) followed by a cued recall (score ranging from 0 to 9) for the forgotten images, performed by giving the name of the category of the missing items. Intrusions are reported for all steps. The sum of the free and cued recall forms the total recall (score ranging from 0 to 9, pathological < 9) [11, 12].

Details of the TNI-93 results have been carefully collected. However, for some patients the different steps of the TNI-93 could not be performed due to the severity of the cognitive and physical impairments. When naming, immediate recall, free recall or total recall was not possible due to the severity of the disorder, we

scored zero as result. When there was no result for the number of encoding attempts or the number of intrusions, we left the result as missing data.

Ethics: Our study was approved by the Local Ethics Committee for the Clinical Research of the Hôpitaux Universitaires de Paris Seine Saint-Denis (Number of protocol: CLEA-2019-93) and according to current French legislation for retrospective studies on file, patient consent was not required.

Statistics: Demographic, clinical and cognitive measures were compared between A + and A- patients, as well as between A + T + and A-T- patients. Fisher's exact test was used for categorical variables and Welch's t-test for continuous variables.

Generalized linear regressions (GLMs) were performed to study the impact of amyloid status adjusted for gender, age, education, MMS and Tau status on TNI subscores.

Same models were performed in order to investigate differences in TNI subscores between A + and A- patients in each cognitive complaint group (memory, language and other), looking at the interaction between amyloid status and cognitive complaint group. The memory and language group was removed from this analysis due to small sample (n = 6).

Similar analyses were performed only on A + T + and A-T- patients.

GLMs with binomial family and logit link were used for TNI naming, TNI immediate recall (IR), TNI free recall (FR), TNI total recall (TR); and GLMs with Poisson family and logarithm link were used for TNI number of encoding attempts, TNI encoding intrusion and TNI recall intrusion. Corrections for multiple comparisons were performed using Benjamini-Hochberg method. For all GLMs, type II F-tests were used. Cohen's f2 were calculated to assess effect sizes. Normality of residuals as well as heteroskedasticity were checked visually. Cook's distances and hat values were calculated to identify influential data. Analyses were run without subjects with Cook's distances higher than 1.

Receiver Operating Characteristic (ROC) curves were performed on TNI subscores to discriminate A + and A- patients. Optimal cutoffs were measured by maximizing sensitivity and specificity indicator.

Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results are expressed as mean ± standard deviation (SD) and percentage.

Results:

A total of 108 patients were included (Table 1, Figure 2). Among the 108 patients, 67 had a memory complaint, 19 a language complaint, 6 had both memory and language complaint and 16 had another complaint (behavioral disorder, hallucination...). Mean age of the population was 66.9 ± 8.5 years old and 51% were women. Mean education level was 8.9 ± 5.16 years, illiterate patients represented 27% of

the population, French was the native language for 47% of patients and mean MMSE score was 17 ± 5.48 (Table1). All patients had a brain imaging. 91 patients had a cerebral MRI, 89 patients had a PET scan.

Patients were classified into two groups according to the ATN criteria: there were 80 patients in the A+ group, corresponding to patients with amyloid abnormalities and 28 in the A- group, corresponding to patients without amyloid abnormalities. Patients in A+ group were clinically defined as having AD (n=53 patients), Lewy body dementia (LBD) (n=12 patients), both diseases (LBD and AD n=2), vascular dementia (n=4), mixed dementia (vascular and AD disease, n=3), fronto-temporal dementia (n=2), semantic dementia (n=2), Parkinson's disease dementia (n=1) or corticobasal dementia (n=1). In A- group, patients were clinically defined as having psychiatric disorders (n=6 patients), fronto-temporal dementia (n=7), normal pressure hydrocephalus (n=2), vascular dementia (n=4), semantic dementia (n= 3), LBD (n= 2), sequelae of inflammatory pathology of the central nervous system (n=1), vitamin deficiency (n=1) and progressive supranuclear palsy (n= 2).

1. Comparison of A+ and A- patients

1.1 Whole group of patients (Table 1)

Age, gender and education did not significantly differ between A+ and A- groups. MMSE score was significantly more altered in A+ than in A- group (A+: 16.2±5.0; A-: 19.2±6.2; p=0.01).

Regarding TNI-93 scores, patients from the A+ group (N= 80) were significantly more impaired than patients from the A- group (N=28) on immediate recall (A+: 5.9±2.8; A-: 7.4±2.6; p=0.001), free recall (A+: 3.5±2.7; A-: 5.9±2.8; p< 0.001) and total recall (A+: 5.7±3.5; A-: 7.8±2.8; p< 0.001) (Table2) and on number of intrusions during the recall phase (A+: 1±1.8; A-: 0.1±0.3; p=0.002). We found no differences between both groups in naming, number of encoding attempts and intrusions during encoding.

Table 1. Comparison between A+ and A- patients

	all N=108	A+ N=80 (74.07%)	A- N=28 (25.93%)	Pvalue ‡
Age	66.93 ± 8.49	67.86 ± 7.53	64.28 ± 10.50	0.054
Gender (*F*)	55 (50.93%)	42 (52.50%)	13 (46.43%)	0.663
Education (*years)*	8.89 ± 5.16	8.81 ± 5.03	9.11 ± 5.61	0.796
Native language (*French*)	51 (47%)	40(50%)	11 (39%)	
Illiterate	29 (26.85%)	20 (25.00%)	9 (32.14%)	0.467
Disease duration (*years*)(Y)	2.38 ± 2.86	2.27 ± 2.11	2.71 ± 4.39	0.489
MMSE (/30)	**17.00 ± 5.48**	**16.20 ± 5.02**	**19.29 ± 6.17**	**0.010***
Motif				
memory	67 (62.04%)	52 (65.00%)	15 (53.57%)	
language	19 (17.59%)	14 (17.50%)	5 (17.86%)	
memory+language	6 (5.56%)	6 (7.50%)	0 (0.00%)	
others	16 (14.81%)	8 (10.00%)	8 (28.57%)	0.069
Tau	**52 (48.15%)**	**50 (62.50%)**	**2 (7.14%)**	**<0.001***
Denomination	7.81 ± 1.91	7.78 ± 1.94	7.93 ± 1.88	0.883
Immediate recall	**6.25 ± 2.80**	**5.85 ± 2.77**	**7.39 ± 2.59**	**0.001***
Number of encoding §	2.04 ± 0.89	2.22 ± 0.90	1.54 ±0.65	0.287
Encoding intrusion §	0.96 ± 1.48	1.10 ± 1.46	0.58 ± 1.50	0.309
Free recall	**4.14 ± 2.59**	**3.54 ± 2.67**	**5.86 ± 2.84**	**<0.001***
Total recall	**6.24 ± 3.43**	**5.68 ± 3 .47**	**7.82 ± 2.82**	**< 0.001***
Recall intrusion §	**0.75 ± 0 .61**	**1 ± 1.84**	**0.12 ± 0.33**	**0.002***

Notes. Data are given as mean ± standard deviation for continuous variables and as count (percentages) for categorical variables.

‡ Welch's t-test was used to compare groups for continuous variables and Fisher's exact test for qualitative variables. For TNI subscores, p values were extracted from GLMs and thus, were adjusted for age, gender, education, MMS and Tau status. They were corrected from multiple testing using Benjamini-Hochberg correction.

§ GLMs with Poisson family and logarithm link and GLMs with binomial family and logit link otherwise.F: female, Y: years, m: mean, SD: standard deviation, Tau: presence of phosphorylate Tau, *: statistically significant.

1.2 TNI-93 scores in subgroups according to clinical presentation (Figure 3)

In the subgroup of patients with memory complaint (N=67), A+ patients (N=52) were significantly more altered than A- patients (N=15) on immediate recall (p<0.001), free recall (p< 0.001) and total recall (p< 0.001). A+ patients had also significantly more intrusions during recall than A- patients Naming, number of encoding attempts and intrusions during encoding did not differ between both groups. To sum up, similar results were observed in the memory subgroup than in the whole group of patients, and a similar tendency was observed in the language subgroup.

In the subgroup of patients with presentation other than memory complaint (ie language impairment or others presentation such as behavioural and hallucination), we observed no difference between A+ and A- patients on the TNI-93 scores.

2. Comparison of TNI-93 scores in A+T+ patients and A-T- patients (Table 2)

A+T+ patients (N=50) were significantly more impaired than A-T- patients (N=26) on immediate recall (p<0.001), free recall (p<0.001) and total recall (p<0.001). A+T+ patients also had significantly more intrusions during recall than A-T- patients (p<0.001), more encoding attempts (p=0.049), and more intrusions during encoding (p=0.038). There was no difference between A+T+ and A-T- patients in naming.

Table 2: Comparison of TNI-93 score between patients from A+T+ group and A-T- group

	A-T- N=26 (34.21%)	A+T+ N=50 (65.79%)	Pvalue corrected
Denomination	7.85 ± 1.93	7.54 ± 2.05	0.941
Immediate recall	**7.69 ± 2.22**	**5.42 ± 2.82**	**<0.001***
Number of encodage §	**1.52 ± 0.65**	**2.38 ± 0.86**	**0.049***
Encodage intrusion §	**0.52 ± 1.50**	**1.25 ± 1.12**	**0.038***
Free recall	**6.12 ± 2.69**	**3.44 ± 2.65**	**<0.001***
Total recall	**8.15 ± 2.44**	**5.51 ± 3 .19**	**<0.001***
Recall intrusion §	**0.12 ± 0.34**	**1.24 ± 2.19**	**<0.001***

Notes. Data are given as mean ± standard deviation. P values were extracted from GLMs and thus, were adjusted for age, gender, education and MMS. They were corrected from multiple testing using Benjamini-Hochberg correction.

§ GLMs with Poisson family and logarithm link and GLMs with binomial family and logit link otherwise

*: statistically significant

3. ROC curves

Analyses of the ROC curves revealed that the best scores of the TNI 93 test to discriminate A+ patients from A- were immediate recall (Area under curve (AUC): 0.70), free recall (AUC: 0.74) and total recall (AUC: 0.74) (Figure 4). An immediate recall under 6 offered a sensitivity of 54% and specificity of 83%. A free recall under 4 and a total recall under 8 offered respectively a sensitivity of 63% and 72% and a specificity of 77% and 73% (Table 3).

Table 3. Results of the ROC curve analyses to discriminate A+ and A-

	optimal cutpoint	accuracy	sensitivity	specificity	AUC
omination	8	0.55	0.54	0.57	0.55
ıediate recall	6	0.62	0.54	0.83	0.7
ıber of encoding*	3	0.57	0.44	0.93	0.73
oding intrusion	1	0.61	0.54	0.79	0.66
; recall	4	0.66	0.63	0.77	0.74
ıl recall	8	0.72	0.72	0.73	0.74
all intrusion	1	0.52	0.37	0.89	0.64

* numbers of trials at encoding.

Discussion:

In this study, we assessed the diagnostic value of the TNI-93 to discriminate A + patients and we showed, in a group of patients presenting with cognitive complaint, that immediate recall, free recall and cued recall were more impaired in A + patients that in A- patients. This was particularly significant in patients presenting with memory complaint. ROC curves showed that they are sensitive and specific scores of the TNI-93 to distinguish AD patients from non-AD patients.

Limitations

Our study has some limitations. First, in the main analysis, we compared A + patients with A- patients. The presence of an amyloid peptide abnormality does not define AD properly, but it is evocative of an amyloid pathology. There is a continuum between amyloid disorder and AD, and amyloid peptide abnormality precedes Tau pathology and neuronal loss AD [26]. To verify our results in patients with clear diagnostic criteria, we compared a subgroup of patients with AD biological criteria (A + T+) with A- T- patients who did not have Tau or amyloid pathology. These analyses showed similar results than the main analysis, with a slight significant increase.. Hence, the alteration of immediate, free and total recall on the TNI-93 might be an early sign of AD, specific of amyloid pathology rather than Tau pathology.

Additionally, we used the A T N criteria developed by the NIA - AA in 2018 [14] to classify patients with abnormalities secondary to a continuum of AD (A+) and patients with or without pathological modification but not secondary to AD (A-). Other diagnostic criteria could have been selected such as the IWG criteria [2] or the 2011 NIA-AA criteria [14]. However, both are based on the cognitive and clinical assessment of patients. They seemed less relevant to our approach and difficult to use in a retrospective study without being a source of bias due to the difficulty of collecting and transcribing clinical data. We chose the NIA- AA 2018 criteria [14] since they are objective and independent from the clinical evaluation. Hence, the diagnosis of AD in this study does not rely on neuropsychological tests notably on the TNI-93. This would have led to a circular reasoning which is also a source of bias.

The diagnoses performed with the ATN criteria were sometimes different from the clinical diagnoses retained during the weekly meetings of neurologists, neuropsychologists and radiologists at Avicenne

hospital. In the A + group (n = 80), 70 patients had a concordant clinical and ATN diagnosis of AD (n = 53) or associated pathology (n = 17, LBD and mixed AD + other pathology). In the A- group (n = 28), only one patient had a clinical diagnosis of AD but with a normal CSF profile (no amyloid, Tau or phospho-Tau disorder). Objective criteria based on biomarkers limit bias and are easily reproducible, but they do not consider the patient's semiology as a whole and lack nuances.

Finally, our patient population was not entirely representative of patients with AD. Hence, the female predominance was less obvious than in other AD studies [16–18] and our patients were younger (mean age 66.9 years; literature mean age > 75 years), less educated (mean: 8.9 years ; literature: 12 years) [16] and had a lower MMSE score (17; literature: > 23) [17]. This may indicate a selection bias that could be explained by the inclusion criteria of our study. Indeed, we included only patients who underwent a LP, which is mainly prescribed in patients under 65 years old and/or patients presenting with complex semiology. Additionally, these characteristics may be explained by the multicultural background of our patient population [10]. Our population pool belonged to the "Seine Saint Denis" French department which is one of the poorest and most multicultural department in France with a high rate of population who immigrated and who did not attend school or dropped out at a young age (INSEE) [10].

TNI-93 and Education

The specificities of our patient population demonstrate that the TNI-93 test is suitable for most patients [12], including illiterate patients because the test does not involve reading or writing as well as multicultural patients because it can easily be performed with a translator. In the GLMs, the TNI-93 scores did not correlate with the level of education as it has already been demonstrated by Maillet et al (2016) [12]. It suggests that the test is not impacted by education, and can be used in high or low educated patients. As it is a quick and easy to understand test, it is also accessible to most patients with severe dementia syndrome [11, 12].

Alteration of recall in A + patients

According to ROC curves, the best subscores of the TNI-93 to discriminate A + patients from A- were the immediate recall (AUC: 0.70), free recall (AUC: 0.74) and total recall (AUC: 0.74). The three scores had an AUC > 0.7. Lowering the thresholds of the TNI-93 that were previously defined for the diagnosis of dementia [11, 12] from 6 to 4 for the immediate recall, and from 9 to 8 for the total recall seems to add more specificity for the diagnosis of Alzheimer's disease. A threshold at 6 for immediate recall also offered a good specificity [11, 12].

Alteration of immediate recall in A + patients

Impairment of immediate recall is a deficit in encoding, in spite of the help of semantic indices. This forgetfulness reflects the anterograde memory disorder that appears early and is a source of disability in AD patients [19]. Similar results were observed in studies assessing the diagnostic value of verbal memory cognitive tests such as the Free and Cued Selective Reminding Test (FCSRT) where immediate

recall is decreased in AD patients. However, immediate recall was not the most specific sub-score of the FCSRT for the diagnosis of AD [20, 21].

Although not significant, the number of encoding trials tended to be higher in A + patients compared to A- patients. The increased number of encoding attempts reflects a slowdown in overall information and cognitive processing leading to a slowdown in encoding. This appears to be discriminative with a good positive predictive value especially when there are more than two encoding attempts (Table 3). This could reflect what is described in cognitive assessments of AD patients in real life situations, where slowing down and hesitation are observed in the performance of known or unknown tasks [22]. Additionally, slow learning could be an early sign of hippocampal-type cognitive impairment before the onset of forgetfulness.

Alteration of free and total recall in A + patients

The deficit in free and total recall reflects a lack of consolidation with an alteration in storage and retrieval not improved by semantic indices (delayed free and total recall). This pattern, and notably the alteration of total recall, characterized by the absence of response to semantic indexes, corresponds to the so-called hippocampal syndrome, which has been described in AD patients [4, 5, 19]. Similar results were observed in studies assessing the diagnostic value of other verbal memory cognitive tests such as the FCSRT or the 5-word test in AD [20, 23]. These tests, as the TNI-93, use reinforced encoding followed by immediate, free and then cued recall [11]. Studies assessing verbal memory tests showed more specificity of total recall in the diagnosis of AD but suggest that free recall is more sensitive [20, 23].

Interestingly, we showed here that although the alteration of total recall was specific of amyloid pathology (Specificity of 73% with a cut off score of 8), the alteration of free recall was at least as specific of the amyloid pathology (specificity of 77% with a cut off score of 4). Our results regarding the free recall might be due to the design of the test, to the specificities of our patient population, that is less educated, but also to the short delay between encoding and recall (20 seconds). Because of this short delay, free and total recall may partly reflect encoding processes rather than storage and retrieval. For this reason, it might be interesting to assess the diagnostic value of a delayed recall of the TNI-93 items 20 minutes after encoding.

There were significantly more intrusions during free and total recall in the A + group. Similarly, more intrusions were observed during recall of other verbal memory tests in A + patients compared to A- patients [21, 24, 25]. A study comparing the TNI-93 to the gold standard FCSRT [20] would be interesting to verify that both tests assess the same component of episodic memory.

However, compared to the FCSRT, the TNI-93 is a quick and easy to explain test. It is therefore easy to use during medical consultation. The TNI-93 is also compatible with illiteracy and it can be used in a larger patient population than other verbal memory tests.

Results according to population specificities

The TNI-93 test was not informative in patients with language or other complaints than memory complaint, notably because naming difficulties impact all other scores of the tests and lead to interpretation difficulties. Alternatively, the absence of difference in the language subgroup might be due to a lack of power, due to the small sample of this subgroup (n = 19). Indeed, in the language group, there was a tendency towards a difference between A + and A- patients in immediate recall, free recall and total recall.

Finally, our results on TNI-93 subscores were significant regardless of level of education, Tau's status and MMSE score. The TNI 93 subscores did not correlate with the Tau status but they did correlate with amyloid status. This suggests it is a specific test of amyloid pathology.

Conclusion

We showed that the TNI-93 is suitable regardless of education level, with good value of immediate recall, free and total recall for the diagnosis of amyloid pathology suggestive of AD.

Abbreviations

AD: Alzheimer disease

LP: lumbar puncture

CSF: cerebrospinal fluid

AUC: Area under curve

MMSE: Mini-Mental State examination

CR: cued recall

GLMS: Generalized linear regressions

IR: immediate recall

FR: free recall

TR: total recall

ROC: Receiver Operating Characteristic

LBD: Lewy body dementia

FCSRT: Free and Cued Selective Reminding Test

Declarations

Ethics: Our study was approved by the Local Ethics Committee for the Clinical Research of the Hôpitaux Universitaires de Paris Seine Saint-Denis (Number of protocol: CLEA-2019-93) and according to current French legislation for retrospective studies on file, patient consent was not required.

Consent for publication: All co-authors are agreed for publications.

Data availability statement: All the data are available and will be provided on request by the corresponding author.

Conflict of Interest: The authors have no conflicts of interest in connection with this article.

Study funding: none

Authors' contributions:

CF participated in conception, organization, execution of the research project and data collection, design and execution of statistical analysis and wrote the first draft.

JP participated in the execution of the research project and data collection, and reviewed the results and the manuscript

CBelin, DM, CP, BD and JD reviewed the statistical analyses and the manuscript

CBereaux participated in the execution of the research project and data collection, and reviewed the results and the manuscript

MH participated in the statistical analysis, and reviewed the manuscript.

BG participated in conception, organization, execution of the research project, design and execution of statistical analysis, reviewed the results and the manuscript.

EBA participated in data collection and reviewed the manuscript.

Acknowledgements : not applicable

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Figures

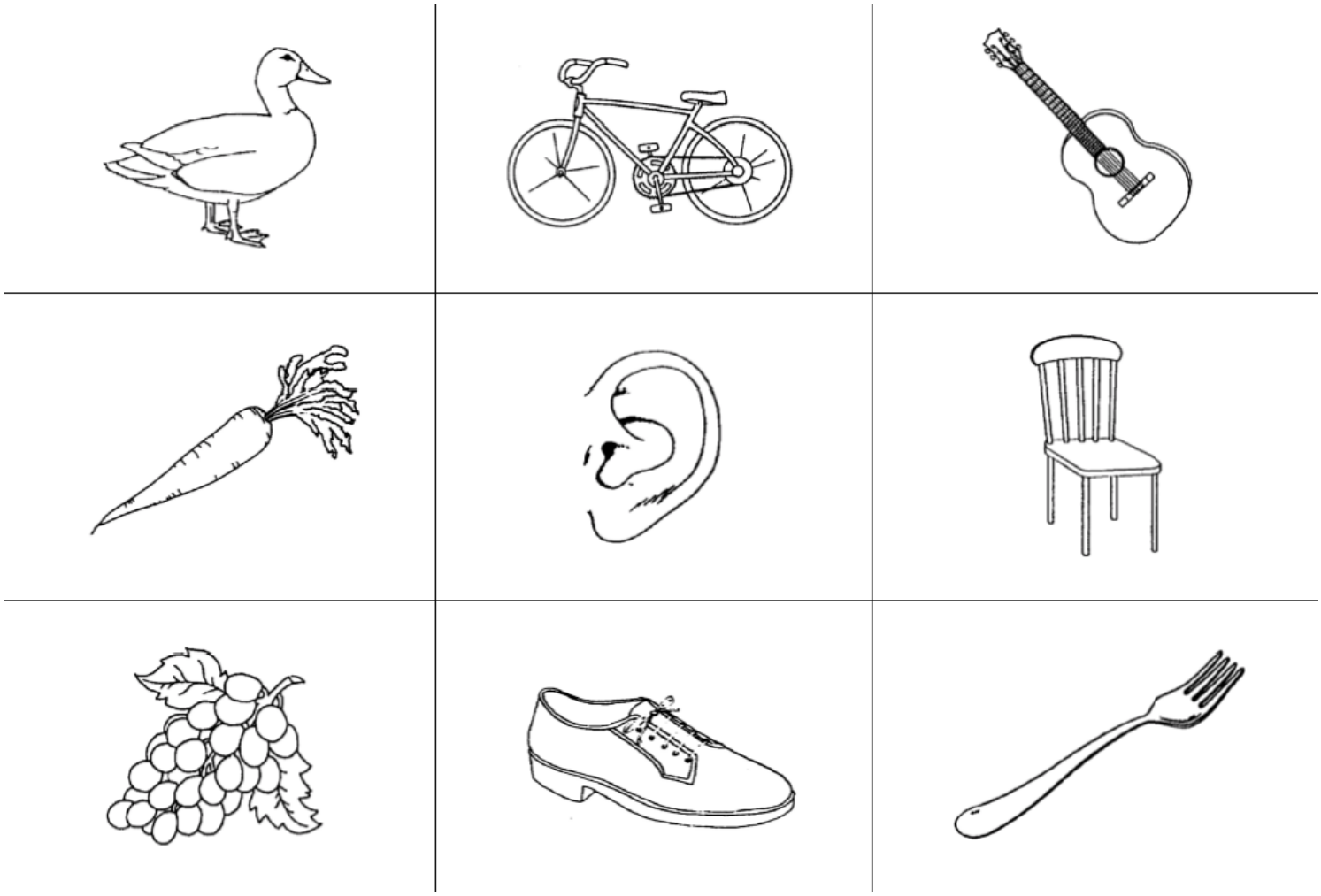

Figure 1

Drawings of the TNI 93 test

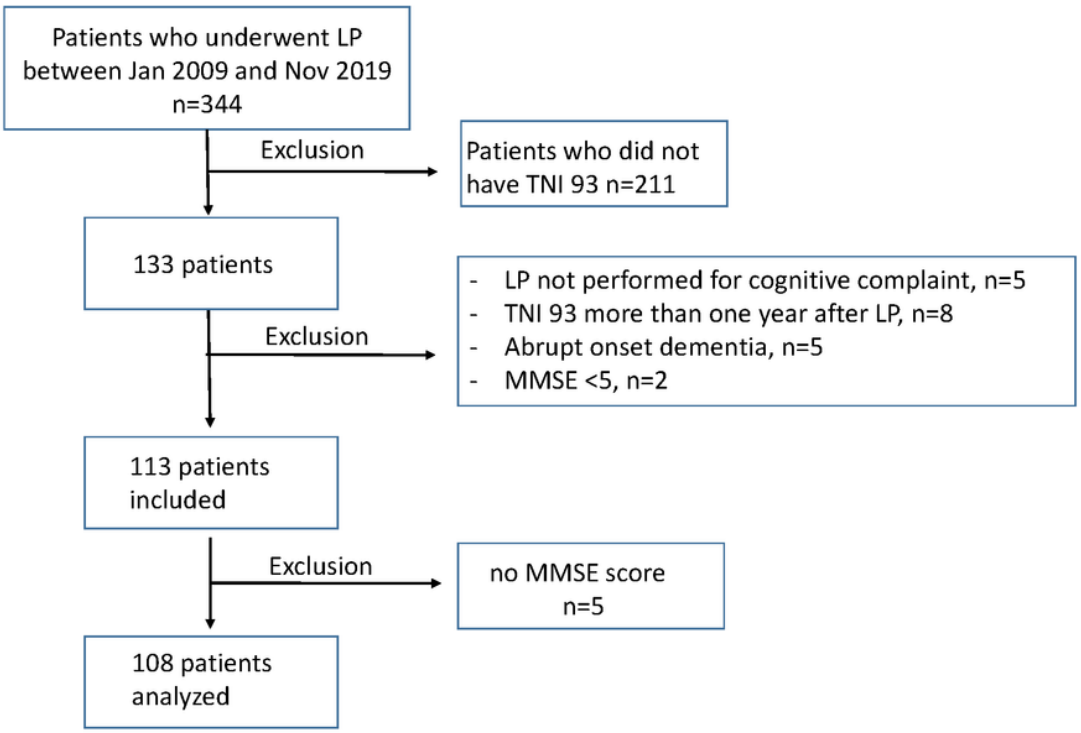

Figure 2

Flowchart of the population screening

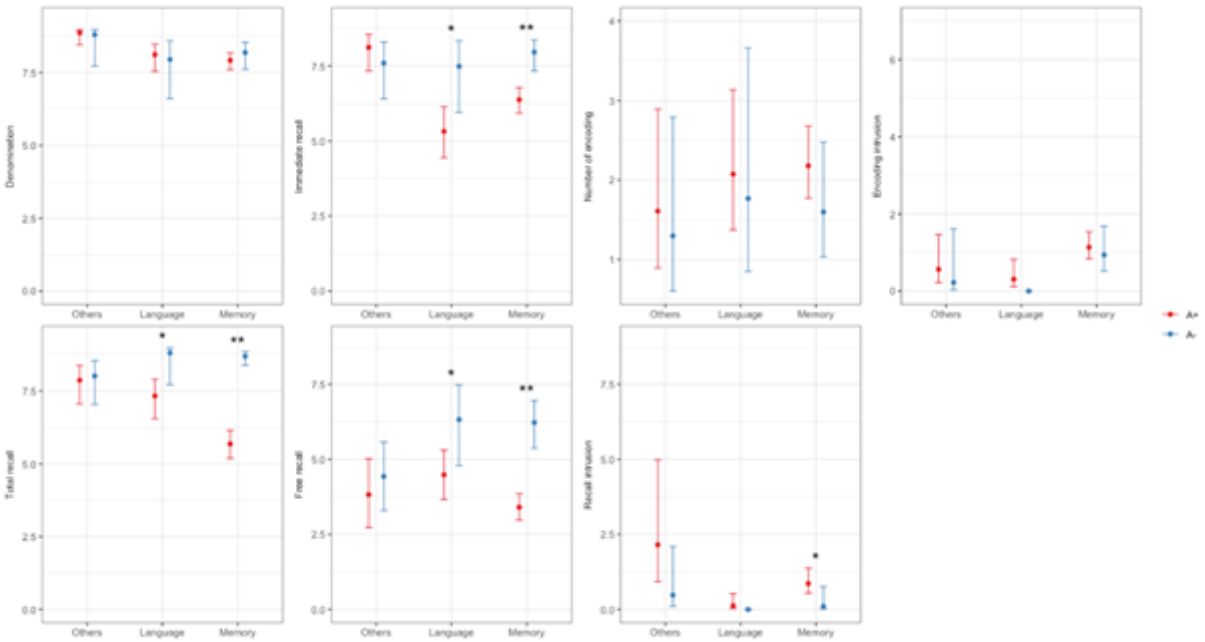

Figure 3

Results at the TNI-93 subscores in subgroups according to the main cognitive complaint. Legend: * significant without correction ** significant after correction.

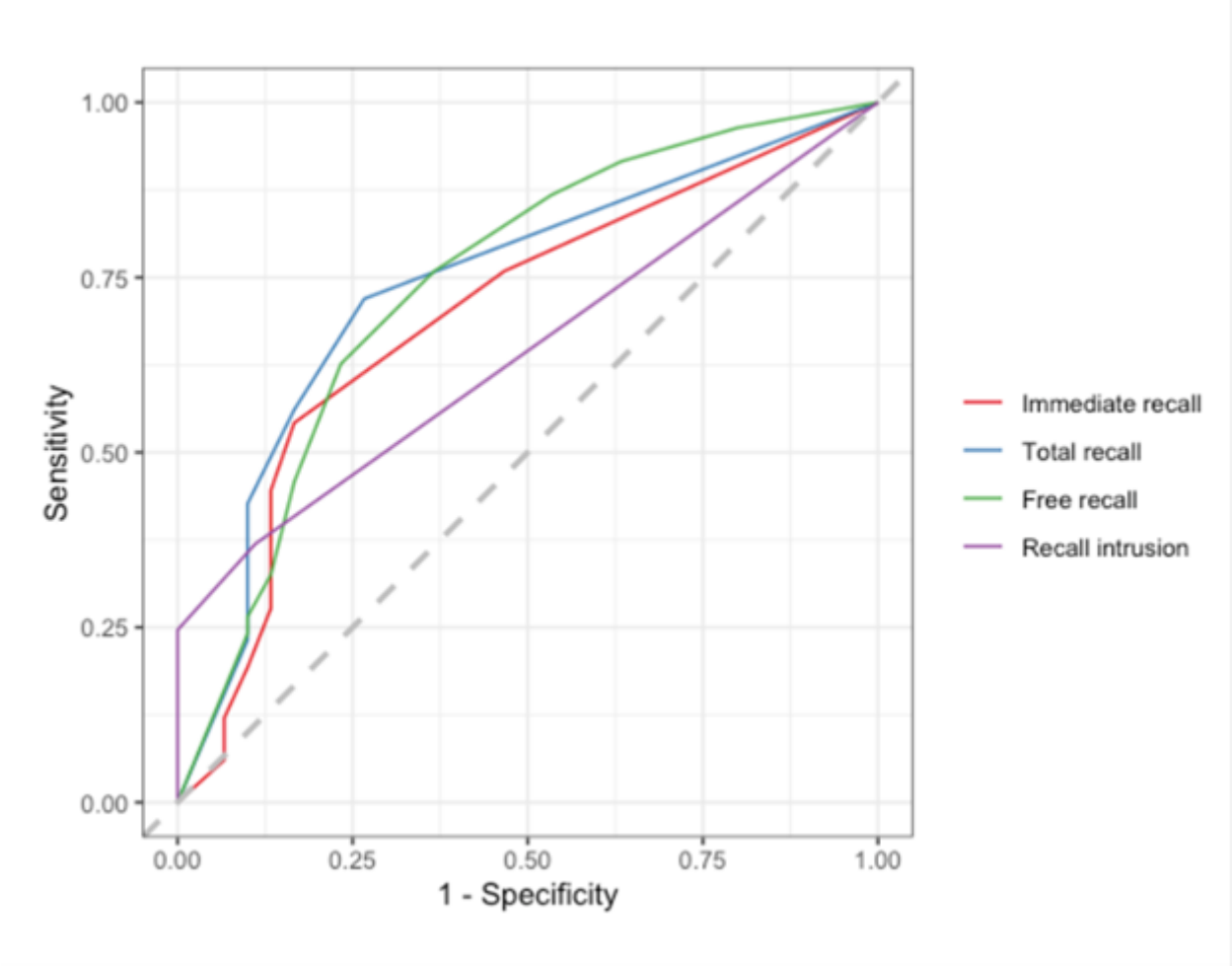

Figure 4

ROC curve analysis to discriminate A+ and A-

Supplementary Files

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- Supplementarymateriel1ThresholdofCSFanalysis.docx