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The Free and Cued Selective Reminding Test: Discriminative Values in a Naturalistic Cohort

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Abstract.
Background: Neuropsychological assessment is still the basis for the first evaluation of patients with cognitive complaints. The Free and Cued Selective Reminding Test (FCSRT) generates several indices that could have different accuracy in the differential diagnosis between Alzheimer's disease (AD) and other disorders.
Objective: In a consecutive series of naturalistic patients, the accuracy of the FCSRT indices in differentiating patients with either mild cognitive impairment (MCI) due to AD or AD dementia from other competing conditions was evaluated.
Methods: We evaluated the accuracy of the seven FCSRT indices in differentiating patients with AD from other competing conditions in 434 consecutive outpatients, either at the MCI or at the early dementia stage. We analyzed these data through the receiver operating characteristics curve, and we then generated the odds-ratio map of the two indices with the best discriminative value between pairs of disorders.
Results: The immediate and the delayed free total recall, the immediate total recall, and the index of sensitivity of cueing were the most useful indices and allowed to distinguish AD from dementia with Lewy bodies and psychiatric conditions with very high accuracy. Accuracy was instead moderate in distinguishing AD from behavioral variant frontotemporal dementia, vascular cognitive impairment, and other conditions.
Conclusion: By using odd-ratio maps and comparison-customized cut-off scores, we confirmed that the FCSRT represents a useful tool to characterize the memory performance of patients with MCI and thus to assist the clinician in the diagnosis process, though with different accuracy values depending on the clinical hypothesis.

Keywords: Alzheimer's disease, dementia, Free and Cued Selective Reminding Test, memory, mild cognitive impairment

INTRODUCTION

The Free and Cue Selective Reminding Test (FCSRT) [1] assesses verbal memory under conditions that control for cognitive processing during encoding and elicits learning and recall by cueing.

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It is one of the most widely used test for identifying the amnestic syndrome of the medial temporal type, although often referred to as a test of 'episodic' memory, it in fact assesses semantic context-free memory rather than contextualized episodic memory with a specific reference to space and time [2]. The FCSRT presents two main advantages when compared to other memory tests. Firstly, the encoding of item is controlled by cueing to rule out attention disorder. Secondly, semantic cueing enhances the information retrieval thus distinguishing between the recall deficit due to frontal lobe dysfunction and the genuine storage deficits that is typical of Alzheimer's disease (AD). This amnestic syndrome, characterized by a poor free recall which is not (or only marginally) improved by cueing, is the core of AD typical presentation [3] even at a prodromal stage [4, 5], also according to the IWG criteria [6, 7] and the JPND consensus [8]. According to research evidence, FCSRT can differentiate patients with AD dementia (ADD) from healthy controls [9], patients with mild cognitive impairment due to AD (MCIAD) [6] from MCI patients who did not convert to dementia [5], as well as MCI patients, including those with 'incipient AD', from healthy controls [10]. Furthermore, the FCSRT was found to differentiate patients with ADD from 1) both vascular dementia (VaD) and behavioral variant frontotemporal dementia (bvFTD) [11], 2) bvFTD [12], 3) prodromal dementia with Lewy bodies (DLB) [13], and 4) progressive supranuclear palsy (PSP), Huntington's disease, and Parkinson's disease dementia (PDD) [14]. However, these data are not conclusive and studies assessing several indices of the FCSRT and their related cut-offs to differentiate AD from other competitive conditions are limited. The published studies so far present, however, some limitations. Firstly, they are mainly focused on the comparison of pre-selected patient groups or cohorts such as in the Lemos et al. study [12], while the clinical usefulness of the FCSRT in the evaluation of an unselected, consecutive naturalistic population accessing a memory clinic because of memory complaints has been poorly investigated. Moreover, the majority of studies focused on each single FCSRT score such as in the Bussè et al. [13] one, while the clinical practice tells us that often the appraisal of a combination of scores is more meaningful.

Indeed, memory impairment due to medial temporal structures does not necessarily underline a diagnosis of AD, as it may be present to some extent in other conditions too. For instance, medial temporal lobe (MTL) atrophy may be found in patients with VaD [15] and semantic dementia [16], and more specifically hippocampal atrophy in Parkinson's disease dementia [17] and bvFTD [18], and a variety of other clinical conditions [19].

Lastly, Teichmann et al. [20] reported that the genuine memory deficit, as measured by the FCSRT, was found in 105 (27%) out of 385 patients with a diagnosis other than AD or depression. Indeed, the FCSRT probes the usefulness of semantic cues to improve recall and characterize the presence of a genuine memory deficit. As reported above, however, it is known that a MTL amnestic syndrome can be observed also in a part of patients affected with other conditions [19].

However, the FCSRT presents with several indices, including measures of free recall, cued recall, facilitation of cueing, and intrusions. These indices could have different accuracy in the differential diagnosis between AD and other competing pathologies, including both neurodegenerative and non-neurodegenerative (e.g., vascular, psychiatric) conditions. Moreover, a given index may not necessarily represent the best performance in every comparison.

In a consecutive series of naturalistic patients, we aimed to evaluate the accuracy of the several FCSRT indices in differentiating patients with either MCIAD [4] or ADD from other competing conditions at their first presentation to a tertiary memory clinic.

METHODS

Patient cohort and diagnosis procedure

We retrospectively selected all consecutive outpatients who presented with memory complaints, for the first time to our University hospital memory clinic in a 4-year period. We selected 501 outpatients, but we only enrolled those who completed the diagnostic process and that were regularly followed-up for at least one year after baseline to have their diagnosis confirmed (or revised) according to clinical follow-up and results of supplementary investigations. Main inclusion/exclusion criteria are listed in supplementary methods.

The final cohort included 434 participants (249 females), aged 43–88 years (mean 74.51 ± 7.46). These outpatients underwent general and neurological examinations, brain magnetic resonance imaging (MRI) (or computed tomography in the case MRI was unfeasible due to contraindications), complete blood and urine screening tests, and neuropsycho-

logical assessment that included the FCSRT. The presence of leukoaraiosis and/or small white matter vascular lesions was not considered as an exclusion criterion.

This cohort was divided into 12 groups according to the diagnosis confirmed at the last follow-up visit 1–6.8 years (mean 2.09 ± 1.23) later, following the current diagnostic criteria. Reportedly 108 patients were diagnosed with ADD and 66 with MCIAD [4]. Among these 174 patients, one-hundred and forty-two patients (82%) performed [F-18] fluorodeoxyglucose positron emission tomography (FDG- 7 PET) and, among them, amyloid PET was also performed in 49 patients and cerebrospinal fluid biomarker assay in other 18 patients. The diagnosis of probable DLB (12 patients), bvFTD (36 patients), probable PSP (7 patients), and probable vascular cognitive impairment (VCI) (23 patients) was based on current criteria [21–24] including the clinical-neuropsychological evaluation and biomarkers such as brain MRI [21–24], FDG-PET for bvFTD [21], [I-123] Ioflupane single photon emission tomography or [I-123] metaiodobenzylguanidine cardiac scintigraphy for DLB [22], and FDG-PET for PSP [23]. Sixty-nine subjects presented phenotypic features suggesting a possible organic disorder as the basis of their cognitive impairment but in whom the neurologic work-up was normal and the final diagnosis turns out to be psychiatric, i.e., mild-to-moderate depression (DEP), 19 patients with various etiologies (miscellaneous) (MISC), 13 with other minor psychiatric disorders (PSYCH) (such as minor anxiety disorders with cognitive complaints), 11 with suspected non-Alzheimer pathology (SNAP), and 41 subjects had subjective cognitive decline (SCD). Twenty-nine patients were affected with MCI of undetermined origin (unclassified MCI, unclMCI); this diagnosis occurred when the clinician was not confident enough to label the MCI syndrome as due to a specific condition. The MISC group mainly included patients with idiopathic REM sleep behavior disorder, sleep apnea syndrome, or essential tremor with cognitive complaints. The PSYCH group was mainly composed of patients with minor affective disorders. All subjects signed an informed consent in accordance with the Declaration of Helsinki.

Cognitive testing

All subjects underwent a full neuropsychological assessment during the initial work-up, which included the Mini-Mental State Examination (MMSE), the FCSRT (Italian word version of the FCSRT-16 [25]) and other cognitive tests evaluating memory, attentional, executive, visuospatial, and language functions. The seven indices of FCSRT were computed: 1) the total number of words recalled in the three immediate free recall trials (IFR score range 0–48), 2) the sum of free and cued recall for each session providing an immediate total recall score (ITR score range 0–48), 3) the delayed free recall (DFR score range 0–16), 4) the sum of the delayed free and cued recall is the delayed total recall (DTR score range 0–16), 5) the recognition phase (RP score range 0–16), 6) the number of intrusion words (IW) during free recall, and 7) the Index of Sensitivity of Cueing (ISC score range 0–1) to evaluate the effectiveness of semantic cues to improve the recovery of stored words. The Index of Sensitivity of Cueing score is the amount of information really encoded despite failure at free recall, and is computed as follows: (immediate total recall score – immediate free recall score)/(48–immediate free recall score).

Statistical analysis

One-way ANOVAs were used to compare age, education, and MMSE score among the 12 groups. Sex distribution was compared by means of the Chi square test. The FCSRT index scores between either ADD or MCIAD group and every other group were compared by using unpaired *t*-test. The *t*-test between diagnostic groups has been applied to underline the coarse differences in FCSRT indexes, whose results are summarized in Table 1. We also combined the ADD and the MCIAD groups to generate an AD group as they share the same underlying pathology. In all the aforementioned analyses, we used the Bonferroni correction to control for multiple comparisons and we set the statistical significance level at p(Bonferroni) <0.05.

We then analyzed the dataset to highlight the role of each FCSRT index and the relationship with the various diagnoses. The analysis consisted of four steps. First, we selected two diagnostic groups; second, for each FCSRT index we computed the AUC value with bootstrap and the balanced cut-off; third, we selected the two most-discriminant FCSRT indexes based on the highest most likely AUC values (statistics given by the bootstrap); fourth, we cycled on every possible choice of the diagnostic groups.

Clearly, the first and the second best index depended on the group pair. We then estimated the

Table 1
Demographic characteristics, MMSE score, and FCSRT index scores of the clinical groups

	Gender M/F	Age (y) M ± SD	Education (y) M ± SD	MMSE M ± SD	IFR M ± SD	ITR M ± SD	DFR M ± SD	DTR M ± SD	ISC M ± SD	RP M ± SD	IW M ± SD
ADD (*n* 108)	42/66	75.55 ± 6.31	9.49 ± 4.25	25.11 ± 2.37	7.46 ± 5.48	22.67 ± 10.70	1.92 ± 2.55	7.31 ± 4.10	0.39 ± 0.22	13.31 ± 2.66	0.50 ± 1.55
MCIAD (*n* 66)	28/38	76.17 ± 5.22	9.82 ± 4.23	26.91 ± 2.37	9.82 ± 7.82	25.85 ± 12.26	2.91 ± 3.48	8.11 ± 4.78	0.46 ± 0.26	13.21 ± 3.30	0.36 ± 0.78
AD (*n* 174)	70/104	76.23 ± 6.47	9.61 ± 4.24	25.79 ± 2.39	8.36 ± 6.55	23.87 ± 11.39	2.29 ± 2.96	7.61 ± 4.37	0.42 ± 0.24	13.27 ± 2.91	0.45 ± 1.31
VCI (*n* 23)	11/12	78.61 ± 5.61	10.52 ± 4.35	27.78 ± 2.43	16.13 ± 9.17*	37.13 ± 10.66*	6.52 ± 4.09*	12.78 ± 4.09*	0.72 ± 0.24*	13.96 ± 3.08	0.13 ± 0.34
DLB (*n* 12)	7/5	77.67 ± 5.18	11.00 ± 3.30	24.58 ± 3.02	16.33 ± 6.55*	40.83 ± 4.99*	7.50 ± 3.09*	14.58 ± 1.62*	0.79 ± 0.12*	15.66 ± 0.65	0.33 ± 0.89
bvFTD (*n* 36)	15/21	74.50 ± 7.18	8.28 ± 4.05	26.06 ± 2.46	12.75 ± 7.27*	32.39 ± 13.09*	4.75 ± 3.76*	11.28 ± 4.70*	0.60 ± 0.27*	14.03 ± 3.07	0.25 ± 0.50
DEP (*n* 69)	19/50	71.90 ± 7.96	9.71 ± 4.58	27.97 ± 2.23	19.52 ± 10.09*	40.06 ± 9.14*	7.81 ± 4.27*	13.36 ± 3.40*	0.78 ± 0.21*	14.97 ± 2.45*	0.28 ± 0.68
PSP (*n* 7)	5/2	75.29 ± 3.30	7.29 ± 3.68	26.57 ± 2.06	13.86 ± 7.01	34.14 ± 11.84	4.71 ± 3.04	11.71 ± 4.39	0.63 ± 0.25	15.57 ± 0.53	0.57 ± 0.98
SNAP (*n* 11)	6/5	75.27 ± 1.85	8.82 ± 4.05	27.73 ± 2.00	8.55 ± 5.22	28.00 ± 11.14	2.73 ± 2.45	9.27 ± 5.08	0.51 ± 0.22	14.18 ± 2.14	0.18 ± 0.40
unclMCI (*n* 29)	13/16	78.25 ± 6.22	9.14 ± 4.7	27.0 ± 1.77	11.83 ± 6.39	31.45 ± 10.76	4.14 ± 3.36	10.28 ± 3.93	0.57 ± 0.24	14.0 ± 2.52	0.31 ± 0.60
MISC (*n* 19)	12/7	71.37 ± 10.28	10.00 ± 4.33	26.74 ± 2.84	16.74 ± 9.45*	36.79 ± 11.46*	6.74 ± 4.34*	11.95 ± 4.58*	0.71 ± 0.26*	15.05 ± 1.99	0.05 ± 0.23
PSYCH (*n* 13)	5/8	68.54 ± 10.10	10.08 ± 3.95	26.62 ± 1.94	19.23 ± 9.16*	38.31 ± 8.79*	7.31 ± 3.75*	12.92 ± 2.72*	0.71 ± 0.21*	15.46 ± 0.97	0.08 ± 0.28
SCD (*n* 41)	22/19	71.63 ± 10.43	11.56 ± 4.27	29.10 ± 1.14	25.37 ± 6.87*	44.59 ± 4.28*	10.29 ± 2.83*	15.12 ± 1.47*	0.87 ± 0.14*	15.78 ± 0.61*	0.37 ± 0.80

ADD, Alzheimer's disease dementia; MCI, mild cognitive impairment; AD, ADD+MCIAD (highlighted in orange); VCI, vascular cognitive impairment; DLB, dementia with Lewy bodies; bvFTD, behavioral variant of frontotemporal dementia; DEP, cognitive presentation of depression; PSP, progressive supranuclear palsy; SNAP, suspected non-Alzheimer's pathology; unclMCI, unclassified MCI; MISC, various etiologies; PSYCH, other minor psychiatric disorders; SCD, subjective cognitive decline; IFR, Immediate Free Recall; ITR, Immediate Total Recall; DFR, Delayed Free Recall; DTR, Delayed Total Recall; ISC, Index of sensitivity of cueing; RP, Recognition Phase; IW, Intrusion Words (DFR phase); *comparison between AD and the other conditions p(Bonferroni)<0.05.

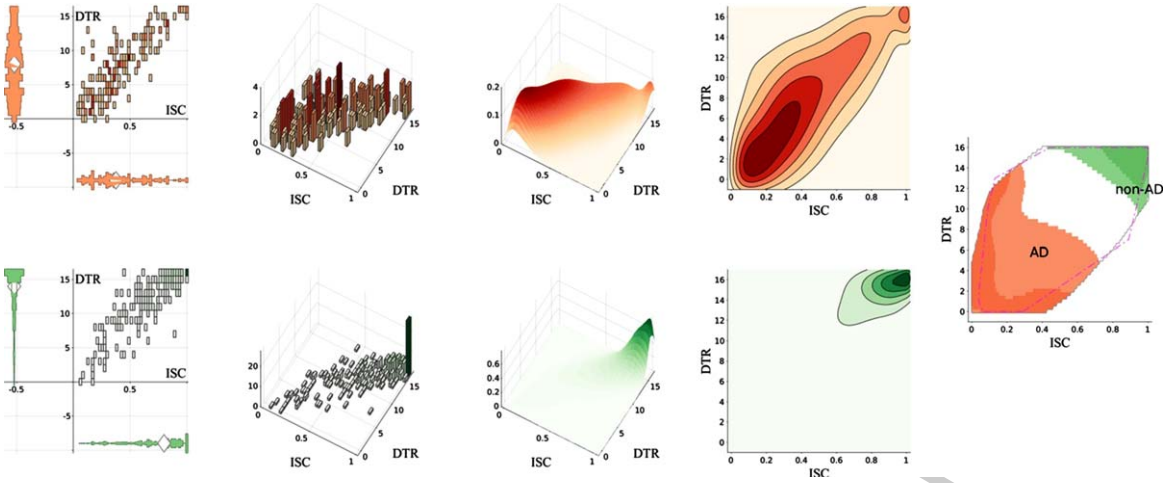

Fig. 1. Transition from FCSRT data to odds-ratio map. From the left to the right: first column: violin plot (data median as diamond marker) and 2D histogram of the AD (ADD and MCIAD) group (top) and all pathologies other than AD (bottom). Second column: 3D representation of the histograms. Third column: kernel-density estimation of the probability density function. Fourth column: contour-plot of the probability density function. Last column: Odds-ratio plot: light shade = odds >2, dark shade = odds >4, gray contour = 99% of all data estimated from the probability density function, purple dashed contour = convex hull of all measured data. DTR, Delayed Total Recall; ISC, Index of Sensitivity of Cueing; AD, Alzheimer's disease dementia (ADD) patients plus patients with MCI due to AD (MCIAD); non-AD, all other patients. This figure shows the conceptual process of the OR plots. We consider here the AD group versus all other patients taken together (non-AD). First, we choose two indexes of the test (here the DTR and ISC) and show the bivariate distribution of the patients together with their marginals over each item (leftmost plots). The same bivariate distribution is displayed as a 3D histogram (second plots column; AD, top row, red; non-AD bottom row, green). The bivariate distribution is transformed into a continuous probability density function with a kernel-density estimation and a Gaussian kernel (the 3D representation in the third plot column). To aid in the visual understanding, the probability density function is displayed flat in 2D with the aid of iso-probability curves (fourth plots column). Finally, the Bayes factor (odds ratio with equal a-priori probability) for the AD and non-AD is computed and displayed with shaded areas of increasing odds (last column).

joint probability distribution for the first and the second best index and we computed the Bayes factor under the hypotheses of flat odds prior (i.e., the posterior odds with two *a priori* equally probable diagnostic hypotheses). A description of the odds-ratio map generation is provided in the supplementary methods.

Figure 1 shows an example of all the results. In that figure we focused on the contrast between AD versus another pathology and test whether the application of the two best discriminating indices of the FCSRT helps in the discrimination. The odds-ratio map was considered as a guideline to assign the diagnostic label with various degree of confidence (odds-ratio >2 and odds-ratio>4). The odds-ratio map is more informative than the cut-off scores as it involves two items (hence taking into account their relationship) and because it shows the area of poor discrimination around a given cut-off.

Finally, all AUC and confidence intervals were computed with a bootstrap method (500 repetitions) and the value used to sort them out was the most likely outcome of the bootstrap.

RESULTS

Demographics, global cognition, and FCSRT indices (Table 1)

No statistically significant differences were found for education ($F_{11,423} = 1.66$, $p < 0.08$) and sex ($\chi^2(11) = 16.466, p < 0.125$) among groups. A significant effect of group was found for age ($F_{11,422} = 4.27$, $p < 0.0001$) and MMSE score ($F_{11,423} = 13.51$, $p < 0.0001$). *Post-hoc* comparisons showed that unclMCI and VCI were older than DEP, MISC, and PSYCH groups ($p < 0.05$) and that MMSE score in ADD was lower than in MCIAD, DEP, unclMCI, VCI, SNAP, and SCD groups. Furthermore, MMSE score in MCIAD was higher than in DLB group and lower than in SCD group ($p < 0.05$).

Table 1 shows the comparisons between AD and every other group. Briefly, the IFR, the ITR, the DFR, the DTR, and the ISC were all significantly lower in AD than in DEP, DLB, bvFTD, VCI, MISC, PSYCH, and SCD groups. Conversely, no FCSRT index was significantly different between AD and PSP, SNAP,

or unclMCI, respectively. The RP score was lower in AD than in DEP and SCD groups while the IW never reached the statistical significance.

The best FCRST index discriminating any two groups

We took into consideration the most accurate FCSRT index, with related cut-off scores derived from the ROC analysis, so to differentiate between couples of groups (Table 2). For clinical purpose we choose to merge ADD and MCIAD together. See the Supplementary Material and Supplementary Table 1 for the results with ADD and MCIAD considered separately. In summary, we found an excellent discrimination capability comparing AD with SCD (IFR), DLB (ISC), and DEP (ITR). A moderate discrimination was instead achieved in the comparison between AD and VCI (DFR), PSYCH (IFR), MISC (ISC), and bvFTD (DTR), respectively, while discrimination between AD and SNAP, PSP, or unclMCI, was unsuccessful.

The forest plot in Fig. 2 shows that some indices are more relevant than others, regardless the contrasting pathology. For instance, IFR and ITR are often selected as the first and second best index, followed by DFR and ISC. Conversely, IW and RP did not provide an adequate discrimination as they were often found not to be statistically significant.

In summary, the ISC, the ITR and the DTR were generally the most useful FCSRT indices to distinguish AD from the other most common forms of cognitive impairment. The best discriminating FCSRT indices for the main pairs of comparisons, are shown in Supplementary Table S with the relative AUC and cut-off scores.

Odds-ratio maps

We explored the discrimination power of the odds-ratio map between AD and the other competing pathologies, when two diagnostic hypotheses are *a priori* and similarly probable. In Table 3, the first and second best two indices to discriminate between two diagnostic hypotheses are summarized, together with the AUC value and the Pearson coefficient between the first and the second best index.

The AUC value for the first best index ranged between 0.669 (DFR; AD versus unclMCI) and 0.940 (IFR; AD versus SCD), while for the second best index the AUC value ranged between 0.664 (IFR; AD versus unclMCI) and 0.934 (ITR; AD versus SCD). The highest AUC value is referred to the comparison between AD and SCD for all indices while the lowest one is related to the comparison between AD and unclMCI. Moreover, we found an excellent accuracy between AD and DLB or PSYCH, respectively. Accuracy was instead moderate when comparing AD and bvFTD, PSP, VCI, or MISC, respectively. The AUC values comparing AD with SNAP did not reach statistical significance.

Figure 3 shows the comparison between AD and either VCI, DLB, FTD, or DEP while the other comparisons are shown in Supplementary Figure 1.

Thus, in the case of *a priori* dual diagnostic hypotheses between AD and each of the aforementioned pathologies, the clinician should take into account the two pertinent FCSRT indices on the odds-ratio map to derive the odds of one or the other probable diagnosis. To note, the two indices change according to the diagnostic hypothesis competing with AD. As an example, Fig. 3B shows the case of a differential diagnosis between AD and DLB, using the ISC and ITR values.

DISCUSSION

Our aim was to evaluate the accuracy of the FCSRT indices applied to a consecutive, naturalistic cohort, while differentiating AD from the main competing disorders in clinical practice, including neurodegenerative, vascular, psychiatric, or uncertain origin.

In the preliminary analysis, our results showed the great utility of the FCSRT in distinguishing AD patients from SCD, DLB, and DEP, while the accuracy versus bvFTD, VCI, PSYCH, and MISC was moderate. Five out of seven FCSRT index scores were significantly lower in AD than in these other conditions, namely the IFR, ITR, DFR, DTR, and the ISC. These results appear to be in line with Teichmann [20] who found that all the FCSRT indices were useful in distinguishing typical AD from the other conditions.

Regarding RP and IW, instead, the AD group performed similarly to the other groups, except for DEP and SCD. Visual recognition deficit has been reported in a part of AD and MCI patients [26], but it can be observed, even if to a lesser extent, also in other dementia, such as bvFTD [27] and DLB [28]. The possible reasons why we did not find significant differences in RP between groups are the slight impairment of RP in the other dementia groups as well, along with the very mild global cognitive impairment (average MMSE = 25.8) of

Table 2
AUC and cutoff score of the best index that discriminated any two groups

	AD	VCI	DLB	bvFTD	DEP	PSP	SNAP	unclMCI	MISC	PSYCH	SCD
AD											
VCI	DFR 0.79[0.66–0.86] 3.03 [1.98–4.69]										
DLB	ISC 0.88 [0.83–0.93] 0.62 [0.58–0.71]	RP 0.59 [0.51–0.75] 15.46 [14.49–15.66]									
bvFTD	DTR 0.73 [0.61–0.80] 10.68 [9.34–11.94]	–	DTR 0.73 [0.57–0.82] 14.54 [11.90–15.17]								
DEP	ITR 0.85 [0.78–0.89] 35.16 [32.34–37.47]	–	–	DFR 0.70 [0.60–0.78] 7.51 [4.54–8.38]							
PSP	DFR 0.74 [0.51–0.85] 3.81 [0.79–4.55]	–	DFR 0.73 [0.51–0.85] 7.34 [3.76–8.31]	–	DFR 0.72 [0.56–0.80] 7.41 [3.44–8.24]						
SNAP	–	DFR 0.74 [0.57–0.87] 4.28 [2.72–6.67]	ISC 0.88 [0.66–0.97] 0.64 [0.60–0.73]	–	ITR 0.81 [0.67–0.90] 35.74 [33.67–40.88]	IFR 0.71 [0.48–0.89] 11.82 [7.17–15.44]					
unclMCI	DFR 0.67 [0.57–0.75] 1.49 [0.99–2.38]	DTR 0.68 [0.55–0.79] 13.61 [12.03–14.52]	DTR 0.80 [0.70–0.89] 13.84 [11.80–14.54]	–	ITR 0.75 [0.65–0.82] 40.71 [36.55–42.28]	–					
MISC	ISC 0.78 [0.65–0.88] 0.59 [0.50–0.68]	–	–	–	–	–	IFR 0.76 [0.58–0.86] 14.08 [8.61–15.70]	DFR 0.68 [0.51–0.80] 5.34 [3.96–7.11]			
PSYCH	IFR 0.83 [0.66–0.92] 12.12 [10.35–15.70]	–	–	IFR 0.68 [0.50–0.83] 17.51 [12.46–20.47]	–	–	DFR 0.82 [0.62–0.92] 4.44 [3.14–6.43]	DFR 0.73 [0.55–0.85] 4.92 [4.09–6.89]			
SCD	IFR 0.94 [0.90–0.97] 15.63 [14.57–17.90]	IFR 0.75 [0.65–0.86] 20.24 [17.58–23.59]	IFR 0.82 [0.69–0.90] 21.82 [18.13–23.29]	IFR 0.87 [0.79–0.92] 19.48 [17.22–21.66]	DFR 0.67 [0.57–0.74] 8.90 [7.62–10.15]	DFR 0.88 [0.71–0.95] 7.79 [6.20–8.56]	IFR 0.95 [0.88–0.99] 16.69 [13.54–18.04]	IFR 0.90 [0.81–0.96] 18.01 [15.55–20.39]	IFR 0.74 [0.60–0.85] 20.54 [17.55–24.24]	DFR 0.71 [0.57–0.85] 8.83 [7.38–10.12]	

The AUC value and the cut-off scores (lower part of the cell) of the index used to compare group pairs with 95% confidence level (CL) computed with a bootstrap method, are showed. The cut-off values were computed by balancing sensitivity and specificity, whereas non-significant comparisons are represented by a dash. Statistical significance was established taking into account the lowest confidence value for the AUC. 95% confidence limits in brackets, AUC and cutoff value of the best index are respectively shown in upper and inferior part of the cell.

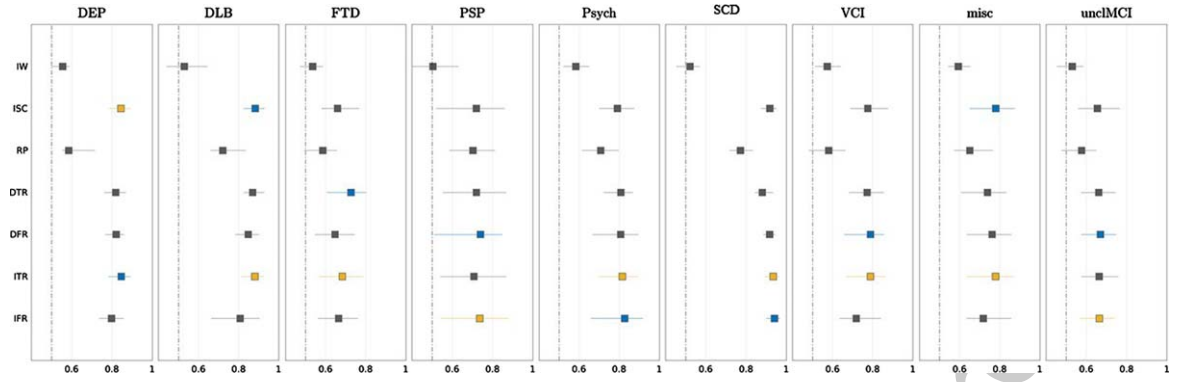

Fig. 2. Forest plot of FCSRT indices with corresponding AUC values in the comparison between AD and other pathologies. In blue the best first index and in yellow the second best index; the dotted line indicates the 0.5 value of the AUC.

AD patients, therefore less likely showing compromised RP. Instead, we found a significant RP difference between AD patients and both DEP and SCD patients. While IW score was found to be particularly indicative of typical AD [20, 29], in our study IW score never reached statistical significance, possibly because we included AD patients with very mild global cognitive impairment (average MMSE score 25.75 ± 2.57), thus rendering intrusions less frequent.

We also failed to find significant FCSRT indices score differences between AD and SNAP, unclMCI, or PSP. As for SNAP and possibly for unclMCI too, this probably occurred because they may share a similar degree of MTL atrophy with AD [30]. As to PSP patients, they can show memory impairment in learning, consolidation, and retrieval process of the information, except in the recognition phase [31, 32]. Moreover, our PSP sample size was very small.

As for the discriminative power of individual indices (Fig. 2), this depends on the specific group comparison and, within the same comparison, many indices are equivalent to each other, so they might be used interchangeably.

A relevant aspect concerns the low scores of FCSRT that we observed in various conditions other than AD, either due to attentional or executive functions deficit or to a genuine MTL memory deficit [33, 34]. Furthermore, the possible presence of cerebrovascular pathology in AD [35], the presence of atrophy within the memory-network in a part of bvFTD patients [34], as well as the explicit memory impairment, partly due to the dysexecutive deficit, in DLB patients [36], potentially confounded the differential diagnosis based on the FCSRT, at least in some patients. Moreover, although our assumption admitted 'pure' conditions as we considered the most likely diagnosis, pathological studies postulate that comorbid pathologies are rather the rule.

Focusing on the comparison between AD and the most common forms of cognitive impairment, i.e., DLB, bvFTD, VCI, and DEP, our findings suggested that FCSRT indices could determine a specific disease-dependent profile with an excellent to moderately good accuracy, providing the alternate use of different FCSRT indices is warranted.

The comparison of the present results, which are predominantly based on varying odd-ratio between couples of pathologies rather than on cut-off scores, with those of previous literature has required the computation of sensitivity, specificity and accuracy of the first and the second best index. This index was based on a balanced cut-off score of our naturalistic sample (i.e., data driven approach).

Grober et al. [37] compared thirty-five patients with ADD and fourteen patients with VaD using the FCSRT picture version and the established cut-off score [38], finding 0.83 sensitivity, 0.21 specificity, and 0.65 accuracy for the IFR index, and 0.71, 0.79, and 0.73 for the ITR index respectively. Those data, even if obtained in a few patients, showed the expected benefit of controlled learning and the important role of frontal and attentional system in the memory task. In our work, using instead the FCSRT word version, the two best indices that discriminate between AD and VCI were found to be the DFR and the ITR scores. Concerning the ITR index, comparable to that used in [37], we found 0.78 sensitivity and 0.70 specificity (accuracy 0.77), thus very similar to their results. All together, these data show that the ITR index has a good accuracy in distinguishing between AD and VCI patients, as in the latter the

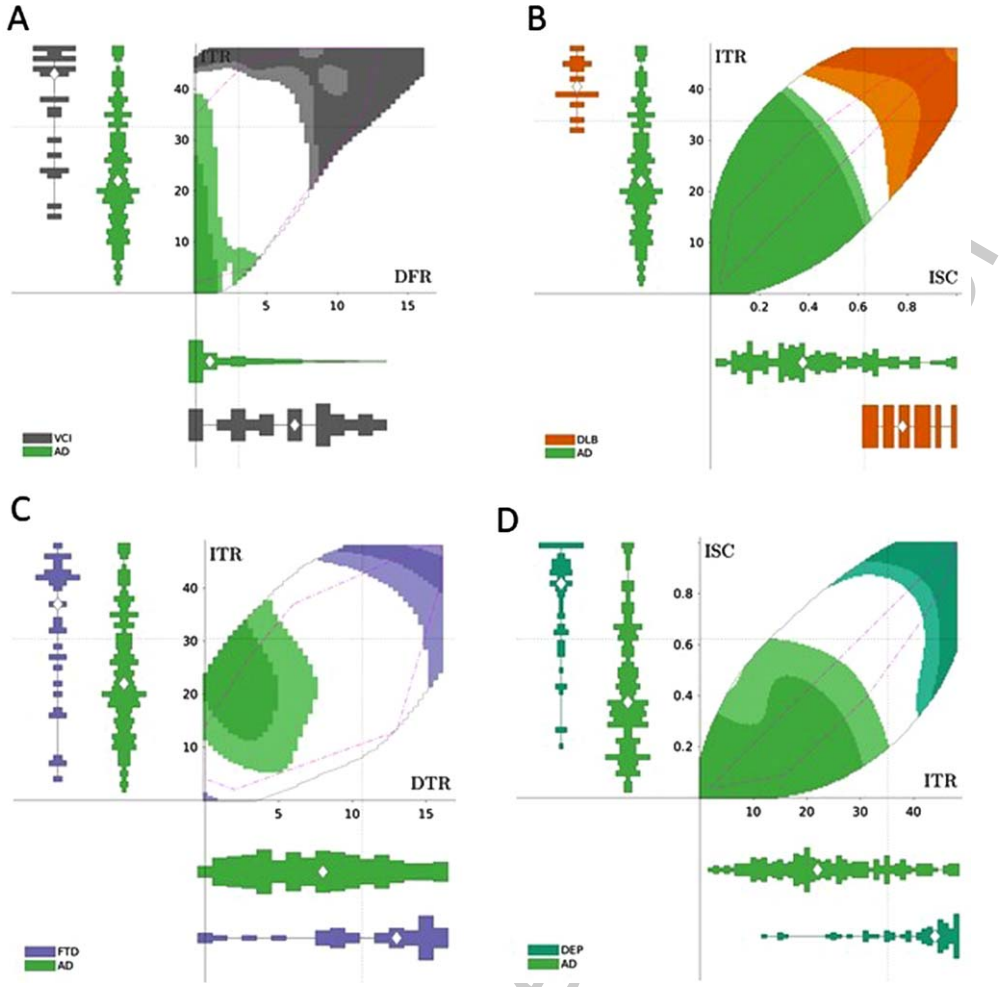

Fig. 3. AD group versus VCI (A), DLB (B), bvFTD (C), and DEP (D) groups. In the x-axis the best index and in the y-axis the second best index to discriminate between two groups. The violet dash dotted line indicates the convex hull of actual data of two groups. The dotted lines indicate the cut-off value of the two indices. The violin plots show the distribution of patients index score. Diamond is the median value. As an example, in B, a patient falling in the dark green area would more likely be classified as an AD patient (OR > 4). The odds-ratio decreases in case the patient would fall in the light green area (OR > 2). The white area is the region of poor diagnostic weight (OR < 2) while the dark and light orange areas refer to a patient more likely affected with DLB.

frontal-like impairment in elaborative encoding and strategic retrieval may benefit from cueing [39].

Lemos et al. [12] compared thirty-two bvFTD and thirty-two AD patients, matched by gender, age, education level, and severity of cognitive decline using the FCSRT word version and the established cut-off score. They found 0.91 sensitivity, 0.71 specificity (accuracy 0.78), for both ITR (cut-off score 27) and DTR (cut-off score 8) respectively. In the comparison between AD and bvFTD we found 0.74 sensitivity, 0.64 specificity (accuracy 0.72) for ITR (cut-off score 32), and 0.78 sensitivity, 0.61 specificity (accuracy 0.75) for DTR (cut-off score 12). Our findings are thus weaker than Lemos' ones [12] but it is worth noting that their AD group was smaller and more severely impaired (MMSE score = 21.22±0.70) than ours (MMSE score = 25.79±2.39). Also, in our study we dealt with a consecutive, naturalistic population and not with *a priori* selected groups. Apart from these differences in accuracy, our data confirm that roughly a quarter of bvFTD patients exhibit a memory impairment overlapping that of AD patients, in line with the finding of medial temporal lobe atrophy in a part of bvFTD patients [40, 41].

Also, Teichmann et al. [20] found higher FCSRT sensitivity, specificity, and accuracy values (1, 0.62 and 0.92, respectively) in distinguishing AD from bvFTD but those data are hardly comparable with

ours as they employed the FCSRT to select AD patients meaning that their sensitivity was 100%.

In DLB, cognitive impairment mainly involves attention, executive and visuospatial abilities with relative preservation of memory, while, the deficit of information retrieval, driven by subcortical-frontal regions, is infrequent at milder stages [28]. Bussè et al. [13] compared DLB and MCIAD patients using the picture version of the FCSRT and found 0.76 sensitivity, 0.79 specificity (accuracy 0.77) for the ISC index, and 0.61 sensitivity, 0.74 specificity (accuracy 0.67) for the ITR index, thus only moderate discriminating values. Our results yielded higher figures as the ISC reached 0.79 sensitivity and 0.92 specificity (0.80 accuracy), and the ITR 0.83 sensitivity and specificity (0.83 accuracy). Thus, most patients with DLB benefit from cues during verbal memory test but about 20% of them may show a MTL amnesic syndrome that cannot be distinguished from that of AD patients. In fact, an MRI study carried out in a large European cohort [42] have shown that significant medial temporal lobe atrophy was found in 17.4% of DLB patients by a visual rating scale, thus consistent with approximately 80% accuracy of the FCSRT. Moreover, the co-occurrence of AD pathology is frequent in DLB that may contribute to explain this figure.

A frequent cognitive symptom in depression is memory deficit [43]. Fossati et al. [44] employed a word version of the FCSRT and found that depressed inpatients showed impaired IFR, with normal ITR and recognition compared to normal controls. Our results shown that ITR and ISC are the best indices to distinguish AD from DEP (AUC 0.84). Executive deficits and lack of initiative of depressed patients can lead to a reduced ability to generate appropriate cues in free recall. On the other hand, cued recall could minimize the effect of impaired attention, inefficient strategies and lack of initiative, typical of depressed patients and in line with neuroimaging studies showing how certain regions of the prefrontal cortex are involved in mood regulation and memory processes [45, 46].

Although the use of cut-off values is a standard method of evaluation in clinical practice, it cannot embed the complexity of the distribution describing the data in a given head-to-head comparison. To exploit the information present in the several FCSRT indices but neglected when using fixed cut-offs, we computed the odds-ratio maps that take into account the peculiarities of statistics in different groups. The odds-ratio improves clinical information and helps the clinicians to determine more precisely whether a patient belongs to one or another clinical category, deciding between two *a priori* equally probable hypotheses. In the differential diagnosis process, this could become a practical clinical method, complementary to the cut-off score, that gives more structured information. Moreover, the odds-ratio maps underline that there is always a significant area of indeterminacy around the cut-off score. To generate the odds-ratio map, we restricted the analysis to the two indices with the best discrimination value. In principle, one could consider the joint probability distribution using all indices of the FCSRT. However, the resulting map would be much harder to read, and we would lose the visual cue of the 2D plot, which could be useful for the clinical use.

Among the strengths of this work, this is to our knowledge the first attempt to build odds-ratio maps that provide an immediate visual position of the two best indices among two *a priori* equally probable hypotheses. Moreover, the analyses were conducted in a naturalistic, consecutive cohort, as presented to a tertiary memory clinic. The monocentric nature of this study ensures homogeneous criteria for patient selection, diagnosis procedures, and clinical follow-up.

One limitation of our work was that, especially for some groups, the results should be taken with caution considering the small number of patients included in these groups, such as PSP, DLB, and SNAP. This limitation deriving from the consecutive enrolment of a naturalistic series. In this view, more data are needed to confirm our findings.

Another limitation of this study is the heterogeneous diagnostic sample size and demographics distribution, conditions which might undermine the significance of the ANOVA. While the relative size of each diagnostic group is suggestive of the typical prevalence in a memory clinics cohort, a more consistent and balanced sample is needed to validate the findings.

Finally, patients affected by AD but in different stages of disease severity (i.e., MCI or mild dementia) were considered both separately (see Supplementary Material) and as a single group. This last choice matches the one done for other pathological groups and is based on the common pathology underlying the cognitive disorder.

In summary, our results show that the FCSRT is a useful tool in distinguishing AD from other competing conditions, with different accuracy values depending on each dual clinical hypothesis. Indeed,

Table 3
Best first and second index to discriminate between any two diagnostic hypotheses with the AUC and the Pearson coefficient between index 1 and index 2

diagn hyp 1*	diagn hyp 2*	index 1	index 2	AUC 1	AUC 2	Pearson r
VCI	AD	DFR	ITR	0.788	0.788	0.808
DLB	AD	ISC	ITR	0.882	0.880	0.984
bvFTD	AD	DTR	ITR	0.726	0.683	0.917
DEP	AD	ITR	ISC	0.845	0.843	0.984
PSP	AD	DFR	IFR	0.739	0.736	0.916
SNAP	AD	–	–	n.s.	n.s.	n.s.
unclMCI	AD	DFR	IFR	0.669	0.664	0.916
MISC	AD	ISC	ITR	0.779	0.778	0.984
PSYCH	AD	IFR	ITR	0.827	0.815	0.846
SCD	AD	IFR	ITR	0.940	0.934	0.846

diagn hyp 1, diagnostic hypotheses 1; diagn hyp 2, diagnostic hypotheses 2; *diagn hyp 1 and 2 are *a priori* equally probable.

although MTL atrophy is crucial in the process of age-related memory loss, this could also be observed in a non-trivial part of patients with other conditions, such as bvFTD, cerebrovascular disease, vascular risk factors, traumatic brain injury, and other clinical conditions, including depression [19].

In conclusion, the FCSRT is an easy-to-administer, inexpensive, non-invasive pencil and paper test. Using tailored indices cut-off scores and, in particular, the more informative odds-ratio maps could, therefore, assist clinicians in the process of differential diagnosis between pathologies with a cognitive presentation.

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SUPPLEMENTARY MATERIAL

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