Social cognition deficits – the key to discriminate behavioural variant frontotemporal dementia from Alzheimer's disease regardless of amnesia?

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Abstract

Relative sparing of episodic memory is a diagnostic criterion of behavioural variant frontotemporal dementia (bvFTD). However, increasing evidences suggest that bvFTD patients can show episodic memory deficits at a similar level as Alzheimer's disease (AD). Social cognition tasks have been proposed to distinguish bvFTD, but no study to date has explored the utility of such tasks for the diagnosis of amnestic bvFTD. Here, we contrasted social cognition performance of amnestic and non-amnestic bvFTD from AD, with a subgroup having confirmed *in vivo* pathology markers.

Ninety-six participants (38 bvFTD and 28 AD patients as well as 30 controls) performed the short Social-cognition and Emotional Assessment (mini-SEA). BvFTD patients were divided into amnestic versus non-amnestic presentation using the validated Free and Cued Selective Reminding Test (FCSRT) assessing episodic memory.

As expected, the accuracy of the FCSRT to distinguish the overall bvFTD group from AD was low (69.7%) with ~50% of bvFTD patients being amnestic. By contrast, the diagnostic accuracy of the mini-SEA was high (87.9%). When bvFTD patients were split on the level of amnesia, mini-SEA diagnostic accuracy remained high (85.1%) for amnestic bvFTD vs. AD and increased to very high (93.9%) for non-amnestic bvFTD vs. AD.

Social cognition deficits can distinguish bvFTD and AD regardless of amnesia to a high degree and provide a simple way to distinguish both diseases at presentation. These findings have clear implications for the diagnostic criteria of bvFTD. They suggest that the emphasis should be on social cognition deficits with episodic memory deficits not being a helpful diagnostic criterion in bvFTD.

Key words: Alzheimer's disease, frontotemporal dementia, episodic memory, neuropsychology, social-cognition, amnesia, differential diagnosis.

Introduction

Relative sparing of episodic memory remains a diagnostic feature of behavioural variant frontotemporal dementia (bvFTD) and is heralded as the neuropsychological gold standard to distinguish bvFTD from Alzheimer's disease at presentation.[1,2] However, increasing evidence suggest that bvFTD patients can show episodic memory deficits,[3] with a subgroup of bvFTD patients being impaired to a similar level as Alzheimer's disease, even in biologically and pathologically confirmed cases.[4,5] Similarly, on a neural level, memory-related structures of the limbic system are found to be affected up to a similar degree as Alzheimer's disease in bvFTD.[3,6-8]

By contrast, social cognition assessments have emerged as powerful new tools to distinguish both diseases in a clinical setting, when CSF biomarkers or amyloid imaging are not available.[9-11] However, it is currently not clear whether the high sensitivity and specificity for social cognition deficits in bvFTD holds regardless of their amnestic impairment when compared to Alzheimer's disease as previous study only investigated social cognition in non-amnestic bvFTD. In others words, in case of severe episodic memory deficits, is assessment of social cognition able to discriminate between the two diseases? The current study addresses this question by contrasting social cognition performance of biologically confirmed amnestic vs. non-amnestic bvFTD as well as Alzheimer's disease patients and healthy controls. We hypothesized that social cognition deficits can distinguish bvFTD from Alzheimer's disease regardless of amnesia.

Materials and methods

Participants

Ninety-six subjects were selected from the database of the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital from September 2005 to June 2012. Twenty-eight typical Alzheimer's disease patients were selected according to the revised NINCDS-ADRDA criteria.[1] Among them, thirteen Alzheimer's disease patients underwent a lumbar puncture showing biological evidence of the Alzheimer's disease pathophysiological process from their CSF biomarker profile defined by a P-Tau/Aß42 ratio greater than 0.21.[12]

Thirty-eight bvFTD patients met the following inclusion criteria: prominent changes in personality and social behavior according to the core clinical diagnostic criteria for probable FTD,[13] clinical progression consistent with the diagnosis of bvFTD (therefore excluding so-called "FTD phenocopies"), frontal/fronto-temporal atrophy at MRI scan and/or frontal/fronto-temporal hypoperfusion at SPECT scan and normal CSF biomarker profile as defined by P-Tau/Aß42 ratio lower than 0.21 when a lumbar puncture was performed (n=17/38, 45%). We included patients with memory impairment if the other core diagnostic criteria of bvFTD were present. Two patients had a genetic mutation (1 GRN, 1 MAPT).

Thirty healthy controls were selected according to the following criteria: normal scores at the MMSE and the FAB, no depression, and no history of psychiatric or neurological conditions. Controls were matched to patients on age and education.

Importantly, all patients were followed-up over at least three years. The clinical progression of every patient was in favour of the initial diagnosis. We did not include participants who presented with the following: (1) clinical or neuroimaging evidence of focal lesions, (2) severe cortical or subcortical vascular lesions on brain MRI, (3) severe depression, or (4) motor neuron disease.

Measurement of CSF biomarkers

CSF samples were collected by lumbar puncture and analyzed for total Tau, Tau phosphorylated at threonine 181 (P-Tau) and Aβ42 using a double-sandwich enzyme-linked immunosorbent assay (ELISA) method (Innogenetics, Gent, Belgium). Assays were conducted at the Metabolic Biochemistry Department of the Pitié-Salpêtrière Hospital, as described elsewhere.[12]

Neuropsychological assessment

All patients underwent a neuropsychological assessment that included the Mini Mental State Exam (MMSE),[14] the Frontal Assessment Battery (FAB),[15] the Free and Cued Selective Reminding Test (FCSRT),[16] the mini-SEA,[9] semantic and morphologic verbal fluencies, digit spans, and a picture-naming task in order to identify semantic memory deficits. In addition, bvFTD patients were tested with the Mattis Dementia Rating Scale (MDRS) and the modified Wisconsin Card Sorting Task (WCST).[17,18]

Assessment of episodic memory (FCSRT)

The FCSRT is based on a semantic cueing method that controls for effective encoding of the list of words and facilitates retrieval by semantic cueing.[16] Immediate cued recall was tested in a first phase in order to control for encoding (16 written words presented in groups of 4x4, maximum score = 16). Then, the memory phase was performed in three successive recall trials. Each recall trial included (1) a free recall attempt consisting of spontaneous recall of as many items as possible, then (2) a cued recall attempt using an orally presented semantic category for items that were not spontaneously retrieved by the patient. The same semantic cues given in the

initial encoding stage were used. This provided (1) a free recall score and (2) a total (free + cued) recall score (/48). Then, after an interval of 30 minutes, a last recall trial was performed, providing (3) a delayed total recall score (/16).

Social cognition & Emotional Assessment (mini-SEA)

The mini-SEA taps into social cognition and emotion disturbances. It consists of two subtests and provides two weighted composite scores: (1) a facial emotion recognition test, scored from 0 to 15, in which participants must identify the emotion expressed in a photograph of a face (happiness, surprise, neutral, sadness, disgust, anger and fear); (2) a shortened version of the Faux-Pas Recognition Test,[19] scored from 0 to 15, which evaluates theory of mind, where participants must detect and explain social faux-pas through short stories. The overall mini-SEA composite score is calculated by adding the two subscores, and scored from 0 to 30. More details about the administration procedure were presented before in a previous study.[39]

Standard protocol approvals, registrations and patient consent.

Controls were included in the INSERM RBM-05-15 study, which was approved by the Ethics Committee of the Pitié-Salpêtrière hospital. Participants provided written informed consent before participating. For all patients, the biological and clinical data were generated during routine clinical work-ups and were retrospectively extracted for the purpose of this work. According to French legislation, explicit informed consent was waived as patients and their relatives were informed that individual data might be used in retrospective clinical research studies.

Definition of bvFTD subgroups

In order to test the ability of the mini-SEA to distinguish amnestic bvFTD patients from Alzheimer's disease, the bvFTD group was divided in two subgroups based on the total recall score of the FCSRT, resulting in A-bvFTD (amnesic bvFTD; n=19; 50%) and nonA-bvFTD (non-amnesic bvFTD; n=19; 50%). The normative data of the FCSRT were employed to compare the total recall score of each patient to its age and educational matched normative group and, consecutively, abnormal scores were defined as scores below the 10th centile.[20] Data of the FCSRT for the bvFTD group and result of this analysis are presented in the Supplementary Material 1.

Statistical analysis

Data were analyzed using SPSS20 (SPSS Inc., Chicago, IL). Prior to any analysis, variables were plotted and checked for normality of distribution using the Shapiro-Wilk test. Parametric data were compared across the four groups (controls, Alzheimer's disease, A-bvFTD, nonA-bvFTD) via ANOVA, followed by Student's t-test. Non-parametric data were analyzed by Kruskal-Wallis ANOVA followed by the Mann-Whitney test for two-by-two comparisons. Cohen's *d* effect-size was computed for all comparisons. Correlations were analyzed using Spearman rank coefficient. Bonferroni's correction for multiple measures was applied for all analyses. Logistic stepwise regression analysis (using the Enter method) and Area Under the Curve were processed in order to determine the accuracy of the mini-SEA to classify each patient in its correct (bvFTD or Alzheimer's disease) group.

Results

Demographics, clinical characteristics and neuropsychological scores

The three groups (controls, Alzheimer's disease, bvFTD) were not significantly different with regard to age, gender and educational level (Table 1). Patient groups did not differ on duration of disease. Not surprisingly, MMSE and FAB scores were significantly lower in the bvFTD and Alzheimer's disease groups compared to controls ($p<.10\text{-}7$). No difference in the MMSE score was observed between bvFTD and Alzheimer's disease, as well as for digit spans (forward and backward), semantic fluency and picture denomination task. FAB and morphological fluency scores were significantly lower in bvFTD compared to Alzheimer's disease ($p<.001$). No difference was observed between bvFTD patients who underwent LP or had a genetic confirmation (n=21/38) and those who did not (n=17/38) for any clinical features and neuropsychological scores (Supplementary Material 2). The same result (ie. no difference for any features or scores) was observed between Alzheimer's disease patients who underwent LP (n=13/28) and those who did not (n=15/28) (Supplementary Material 4).

Demographics, clinical characteristics and neuropsychological executive scores of A-bvFTD and nonA-bvFTD are presented in Table 2. There was no significant difference in age, gender, education, disease duration, MMSE, executive cognitive scores (MDRS, WCST, FAB, verbal fluency), language (picture naming), working memory (forward/backward digit span) between A-bvFTD and nonA-bvFTD patients. A-bvFTD and nonA-bvFTD were respectively 9 and 12 to have a diagnosis confirmation (CSF excluding Alzheimer's disease, or genetic mutation). Within bvFTD subgroups (A-bvFTD and nonA-bvFTD), there was no difference on any demographic, clinical or cognitive measures between patients with and without LP (Supplementary Material 2 and 3).

Episodic memory scores

At the group level, bvFTD patients had significantly higher free recall (p=.10-4; d=0.79), total recall (p<10-4; d=0.83) and delayed total recall scores (p<10-5; d=0.97) than Alzheimer's disease patients (Figure 1). bvFTD and Alzheimer's disease patients did not differ on encoding score. Each FCSRT score of each patient was compared to its age and educational matched normative group. bvFTD patients were 47.4% (n=18/38), 65.8% (n=25/38), 50% (n=19/38) and 42.1% (n=16/38) to have a score below normative scores for, respectively, encoding, free recall, total (free+cued) recall and delayed total recall at the FCSRT. Alzheimer's disease patients were 35.7% (n=10/28, 1 missed data), 85.7% (n=24/28), 85.7% (n=24/28), 75% (n=21/28) to have a score below normative scores for, respectively, encoding, free recall, total (free+cued) recall and delayed total recall at the FCSRT (Supplementary Material 1, Supplementary Table 1). Binary logistic regression using the Enter method using the FCSRT correctly classified bvFTD or Alzheimer's disease with 69.7% of accuracy. AUC for this test (bvFTD vs Alzheimer's disease) was 0.773. ROC curve for the FCSRT is displayed on Figure 1. The overlap between bvFTD and AD on the FCSRT total recall score was 53%.

At the subgroup level, the ANOVA showed significant difference between the three patient groups for all memory scores. More precisely, as expected, A-bvFTD patients performed similarly to Alzheimer's disease patients for each memory scores (table 3, figure 2), although they had significantly lower encoding (p<.10-4; d=1.58), free recall (p<.10-5; d=0.88), total recall (p<.10-7; d=1.21) and delayed total recall (p<.10-7; d=0.87) scores than nonA-bvFTD patients. The nonA-bvFTD patients had higher encoding (p<.10-4; d=1.40), free recall (p<.10-6; d=1.48), total recall (p<.10-7; d=1.67) and delayed total recall (p<.10-7; d=1.51) than Alzheimer's disease patients.

Results were similar when analyses were restricted to bvFTD who underwent LP or had genetic mutation and there were also no differences in the results when contrasting bvFTD who underwent LP or had genetic mutation and bvFTD with clinical diagnosis only, or when the analyses were restricted to bvFTD with clinical diagnosis only (Supplementary Material 2 and 3).

All these analyses were replicated using gender, age then duration of disease as covariates. No effect of these variables was observed and therefore, results did not change. In addition, gender effect was specifically assessed using direct comparison between males and females in each group and no differences were observed.

Social cognition and emotional assessment

At a group level, compared to controls, bvFTD patients had significantly lower scores in both the reduced Faux-pas test and the emotion recognition subtests (all p's<.10-7, with respectively d=2.27 and d=2.61) and therefore a lower total mini-SEA total score (p<.10-7; d=3.27). Alzheimer's disease patients had a lower emotions recognition score (p<.10-4; d=0.91) but showed no significant difference with controls on the Faux-pas test score and on the total mini-SEA score, although a trend was observed for the later (Figure 1; Supplementary Table 2). Compared to bvFTD, Alzheimer's disease patients had higher total mini-SEA (p<10-7; d=2.41), Faux-pas (p<10-7; d=2.09) and emotions recognition (p<10-7; d=1.90) scores. Logistic regression was able to classify patients into bvFTD or Alzheimer's disease in 87.9% of cases when using the mini-SEA total score and in 89.2% or 76.9% in using either the reduced Faux-pas or the emotions recognition score. The results were similar when the analyses were restricted to the patients with CSF/genetic data

(Supplementary Material 2 and 3). The overlap between bvFTD and AD on the mini-SEA score was inferior to 11%.

AUC for the mini-SEA (Alzheimer's disease vs bvFTD) was 0.949. ROC curve for the mini-SEA is displayed on Figure 1.

At the subgroup level (Table 3), ANOVA showed significant differences between the groups. Compared to controls, A-bvFTD and nonA-bvFTD groups had significantly lower scores in both the Faux-pas component (all p values <.10-7; respectively d=2.37 and d=2.60) and the Emotion recognition component (all p values <.10-7; respectively d=2.71 and d=2.56) and therefore a lower total mini-SEA score (all p values <.10-7; respectively d=3.25 and d=3.22). Alzheimer's disease patients had a lower emotions recognition score (p<.10-4; d=0.91) but showed no significant difference with controls on the Faux-pas test score and on the total mini-SEA score, although a trend was observed for the later. A-bvFTD and nonA-bvFTD patients also had significantly lower Faux-pas (respectively p<.10-6; d=2.10 and p<.10-6; d=2.15) and emotions recognition scores than Alzheimer's disease patients (respectively p<.10-6; d=1.92 and p<.10-5; d=1.65), as well as a lower mini-SEA total score (respectively p<.10-7; d=2.40 and p<.10-7; d=2.38). A-bvFTD and nonA-bvFTD did not significantly differ on these measures. Results were similar when analyses were restricted to bvFTD who underwent LP or had genetic mutation and there were also no differences in the results when contrasting bvFTD who underwent LP or had genetic mutation and bvFTD with clinical diagnosis only, or when the analyses were restricted to bvFTD with clinical diagnosis only (Supplementary Material 2 and 3).

Similarly to the analyses conducted on FCSRT scores, analyses for the mini-SEA were replicated using gender, age then duration of disease as covariates. No effect of these variables was observed and therefore, results did not change. In

addition, gender effect was specifically assessed using direct comparison between males and females in each group and no differences were observed.

Accuracy of the mini-SEA to distinguish A-bvFTD or nonA-bvFTD from Alzheimer's disease.

When bvFTD patients were divided on the basis of the presence of episodic amnesia, the mini-SEA has an accuracy of 85.1% to distinguish A-bvFTD patients from Alzheimer's disease and 93.9% to distinguish nonA-bvFTD from Alzheimer's disease.

Finally, in order to confirm the discriminative power of the mini-SEA, we conducted logistic regression analyses using independent random samples from the initial dataset for mini-SEA and FCSRT (Total recall) scores. They are presented in the Supplementary Material and showed very similar results, therefore confirming the sample-based results.

Correlation analyses

Age was set as a nuisance variable in correlations analyses. In Alzheimer's disease, the FAB was significantly correlated to the total mini-SEA score (R=0.60) and the FCSRT free recall (R=0.51). The MMSE was also correlated to the FCSRT encoding score (R=0.47) and the emotion recognition (R=0.47). The digit-span (forward) was correlated to the emotion recognition (R=0.51) and the mini-SEA scores (R=0.64). In bvFTD, the MMSE was significantly correlated to the FAB (R=0.62) and the digit-span (forward) (R=0.48). No other significant correlation was observed.

Discussion

Our results clearly show that social cognition can discriminate biologically confirmed bvFTD and Alzheimer's disease to a high degree. More importantly, social cognition deficits are unrelated to the level of amnesia in bvFTD and thus may provide a uniquely sensitive and specific cognitive marker for the detection of the underlying pathology.

In more details, the preservation of episodic memory in bvFTD has been recently challenged by an increasing number of independent studies showing that bvFTD patients can present with similar levels of amnesia as Alzheimer's disease,[4,5] with both manifesting a combination of frontally mediated and storage-based memory impairment. Although previous studies have suggested that prefrontal cortex degeneration might be the greatest determinant of amnesia in bvFTD,[21,22] more recent evidence suggest that bvFTD patients also show severe atrophy of the medial temporal lobes, including the hippocampus as well as the entire Papez circuit.[4,6] One of the only studies that cross-correlated episodic memory performance with grey matter intensity in bvFTD and Alzheimer's disease showed that posterior parietal and cingulate regions were implicated exclusively in Alzheimer's disease while temporal poles and medial frontal regions were involved specifically in bvFTD.[8] Although the profile of cortical involvement in episodic amnesia is different in bvFTD and Alzheimer's disease, current available episodic memory assessments (i.e. words-list based) may lack of power to differentiate the amnestic form of bvFTD from Alzheimer's disease.[3,5]

By contrast, during the last decade, there has been increasing evidence for the ability of social cognition assessment to distinguish bvFTD from other diseases and specifically from Alzheimer's disease,[23] as it taps into ventral and rostral parts of

the medial prefrontal cortex,[24,25] which are specifically damaged in bvFTD,[26] even at the early stages of the disease.[27] However, the utility of social cognition tasks to differentiate amnestic bvFTD from Alzheimer's disease has not been investigated before. Our findings show that regardless of the presence of episodic amnesia, the mini-SEA can distinguish bvFTD from Alzheimer's disease to a high degree, with a classification power of 87.9% at group level and, more precisely, an accuracy of 85.1% and 93.9% to respectively distinguish A-bvFTD and nonA-bvFTD from Alzheimer's disease. By comparison, the FCSRT lacked of power to distinguish bvFTD from Alzheimer's disease as it was able to classified only 69.7% of patients. The overlap between both groups (53%) was too high to allow an accurate distinction, although bvFTD obtained better performances than AD. By contrast, the overlap between AD and bvFTD using the mini-SEA was low (11%).

Research on social cognition benefits from the increasing recognition that social cognitive processes are crucial for human interactions and adequate social adaptation. A growing number of tests are available to assess the deficits in this domain, which all have different psychometric properties.[28] Theory of mind assessments are particularly useful for capturing the cognitive deficits related to the behavioral symptomatology of bvFTD,[29] but a consensus is needed amidst the numerous available tests. Recently, Bora and colleagues provided crucial findings by conducting a meta-analysis across theory of mind studies in bvFTD and Alzheimer's disease in order to determine the sensitivity and specificity of theory of mind tasks evaluating different processes such as faux-pas recognition, sarcasm detection, false belief and reading the mind in the eyes.[30] Besides replicating previous findings by showing that theory of mind deficits could accurately differentiate bvFTD from Alzheimer's disease, the results showed that faux-pas and sarcasm tests have the

greatest discriminatory potential between both diseases.[31] Moreover, social adaptation also relies on the accurate recognition of other's emotional expressions, a critical process that allows adjusting one's behavior during a social interaction.[32] This process is also impaired in bvFTD and relatively spared in AD during the early stages of the diseases.[33,34,35] This highlights the importance of assessing emotion recognition concurrently with theory of mind. Historically, neuropsychological testing of social cognition relied on long and experimental tasks, which are not always feasible in a clinical setting. The mini-SEA has been designed to provide a quick and easy way to assess theory of mind and emotional recognition through revised and shortened versions of the faux-pas and facial emotion recognition tests.[19,36] This test has been linked, in bvFTD, to grey matter degeneration and perfusion decrease in rostral medial prefrontal cortex,[37,38] and has been shown to accurately distinguish bvFTD from Alzheimer's disease and depression.[9,39]

Our findings have strong implications on a biomarker level. Indeed, current diagnosis of sporadic bvFTD remains challenging, as no biomarkers exist to diagnose the disease. The episodic memory problems in bvFTD further complicate the picture. CSF biomarkers and amyloid imaging showed robust results for identifying Alzheimer's disease relative to controls or patients suffering from FTD.[40] However these investigations rely either on a lumbar puncture, an invasive exam for patients that requires a day of hospitalization, or expensive neuroimaging requiring the production of short-life radioisotopes which require a cyclotron and therefore cannot be performed outside of expert-centers. Similarly, radiological observations of hippocampal volumes have been proposed as a promising specific biomarker for Alzheimer's disease, but recent studies challenged this finding, showing that bvFTD could present with a similar degree of atrophy.[4,6] Short cognitive tests, such as the

mini-SEA, could therefore provide a simple, inexpensive, non-invasive and efficient way to distinguish both diseases at presentation, when facing to a patient with an episodic amnesia that could be an indicator or Alzheimer's disease or bvFTD. This might be in particular relevant for the detection of specific pathology (tau, TDP-43) in bvFTD. For example, a recent study by the Genetic Frontotemporal dementia Initiative (GENFI), a multi-center study on presymptomatic FTD, has shown that genetic predisposed tau patients (MAPT) show severe hippocampal atrophy already up to 10 years before diagnosis.[41] Thus, detection of memory problems in addition to social cognition deficits might be a potential cognitive marker for tau-bvFTD.

On the other hand, the present results raise the question about the specificity of the current framework for the diagnosis of bvFTD. The International consensus criteria for bvFTD proposes the presence of executive deficits with relative sparing of memory and visuospatial functions as neuropsychological features of bvFTD,[13] without any reference to social cognition tests. Considering the increasing evidence of episodic memory impairment in bvFTD, and the diagnostic value of tests that tap into emotional and social abilities, it may be valuable to propose these tests as clinical markers for bvFTD diagnosis.

Although these results are in accordance with previous studies about the clinical relevancy to use social cognition tests to discriminate bvFTD from Alzheimer's disease,[23,28,30] it is important to consider that they could lack of power to distinguish the minority of bvFTD patients that have an Alzheimer's disease underlying pathology. Because it taps into fronto-medial dysfunctions, the mini-SEA has shown to be impaired in those very specific cases.[42] Furthermore, social-cognition performance could be also lower in severe Alzheimer's disease cases, as both theory of mind and emotion recognition performance have been shown to

decrease over the course of Alzheimer's disease as a consequence of a more general cognitive deterioration,[30,34] which was highlighted in this study by the correlation between general cognition and social-cognition performance in Alzheimer's disease. However, we believe that these findings have critical implication on the clinical distinction of bvFTD and Alzheimer's disease in bringing evidence that social cognition could accurately distinguish bvFTD from Alzheimer's disease, regardless of amnesia.

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Demographics and clinical data	Alzheimer's disease	bvFTD	Controls
Nb.	28	38	30
Mean age at test, y	70.3 (11.1)	66.6 (9.3)	67.2 (8.7)
Education, y	11.0 (3.6)	10.9 (3.8)	10.7 (3.7)
Disease duration, y	3.5 (2.8)	2.7 (1.8)	-
Sex, M/F	16/12	24/14	15/15
MMSE (/30)	24.3 (2.7) †	23.4 (3.4) †	29.0 (0.9) *§
FAB (/18)	14.9 (2.0) †*	12.1 (3.3) †§	17.1 (1.0) *§
Nb. of patients with LP	13	19	-
Nb. of patients with genetic mutation	0	2	-
CSF Biomarkers			
CSF Aβ42	311.2 (122.1) *	422.7 (144.1) §	-
CSF Tau	580.4 (255.3) *	241.2 (108.4) §	-
CSF P-Tau	88.1 (32.3) *	39.1 (16.3) §	-
CSF Tau / Aβ42	2.18 (0.9) *	0.84 (0.3) §	-
CSF P-Tau / Aβ42 (cut-off = 0.21)	0.32 (0.1) *	0.09 (0.04) §	-

Table 1 – Mean (SD) scores for Alzheimer's disease, behavioural variant frontotemporal dementia (bvFTD) and control groups on demographics, general cognitive tests and clinical data.

Abbreviations: y= years; MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery: LP: Lumbar Puncture; CSF: Cerebro-spinal fluid biomarquers;

*Significant difference compared to bvFTD.

†Significant difference compared to Controls.

§Significant difference compared to Alzheimer's disease.

	A-bvFTD	nonA-bvFTD
No.	19	19
Mean age at test, y	66.5 (8.8)	66.6 (10.1)
Education, y	10.4 (4.2)	11.4 (3.5)
Disease duration, y	2.7 (1.8)	2.8 (1.9)
Sex, M/F	11/8	13/6
MMSE (/30)	22.5 (3.8)	24.3 (2.8)
FAB (/18)	11.3 (3.7)	13.0 (2.6)
Executive Neuropsychological scores		
MDRS (/144)	116.3 (16.3)	124.4 (11.5)
Verbal Fluency (morphologic)	4.4 (3.5)	7.3 (4.1)
Verbal Fluency (semantic)	9.9 (3.3)	13.4 (4.8)
mWCST category (/6)	2.3 (1.2)	2.8 (4.9)
mWCST perseveration errors	9.2 (7.4)	7.2 (4.3)
mWCST attentional errors	3.4 (2.3)	3.1 (4.3)
Picture naming (%)	94.0 (5.2)	97.0 (4.2)
Digit span forward	4.9 (1.0)	5.7 (1.5)
Digit span backward	3.1 (0.8)	3.6 (1.5)

Table 2 –Demographics data and Neuropsychological scores for A-bvFTD and nonA-bvFTD. Abbreviation: MDRS: Mattis Dementia Rating Scale; mWCST: modified Wisconsin Card Sorting Task; mini-SEA: abbreviated version of the Social cognition and Emotional Assessment. Mean (SD).

FCSRT scores	**Alzheimer's disease**	**A-bvFTD**	**nonA-bvFTD**	**Controls**
Encoding (/16)	13.3 (2.4) †	11.8 (2.9) †	15.2 (0.9) §	-
Free recall (/48)	9.8 (5.7) †	11.8 (8.7) †	18.3 (5.8) §	-
Total recall (/48)	27.8 (11.3) †	30.8 (12.6) †	42.5 (5.2) §	-
Delayed total recall (/16)	7.9 (4.7) †	10.4 (4.8) †	13.9 (3.1) §	-
mini-SEA scores				
Total (/ 30)	24.3 (2.9) †&	16.3 (3.7) *§	16.4 (3.7) *§	25.8 (1.8) †&
Faux-pas (/15)	13.0 (1.7) †&	9.2 (1.9) *§	8.2 (2.7) *§	13.2 (1.5) †&
Emotion recognition (/15)	11.3 (1.7) *†&	7.0 (2.7) *§	8.1 (2.2) *§	12.6 (1.1) †§&

Table 3 – Mean (SD) Free and Cued Selective Reminding Test (FCSRT) and mini-SEA scores for Alzheimer's disease, amnestic (A-bvFTD) or non-amnestic (nonA-bvFTD) behavioural variant frontotemporal dementia and controls.

*Significant difference compared to Controls.

†Significant difference compared to nonA-bvFTD.

§Significant difference compared to Alzheimer's disease.

&Significant difference compared to A-bvFTD

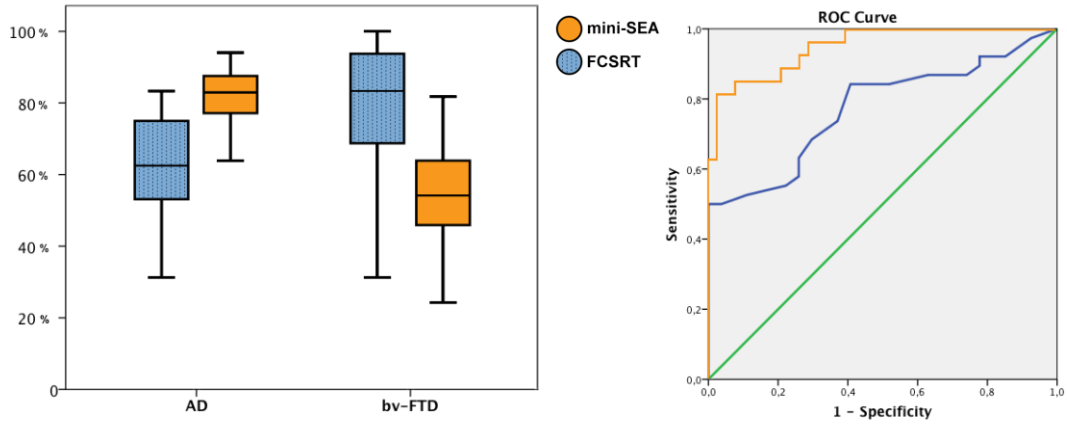

Figure 1

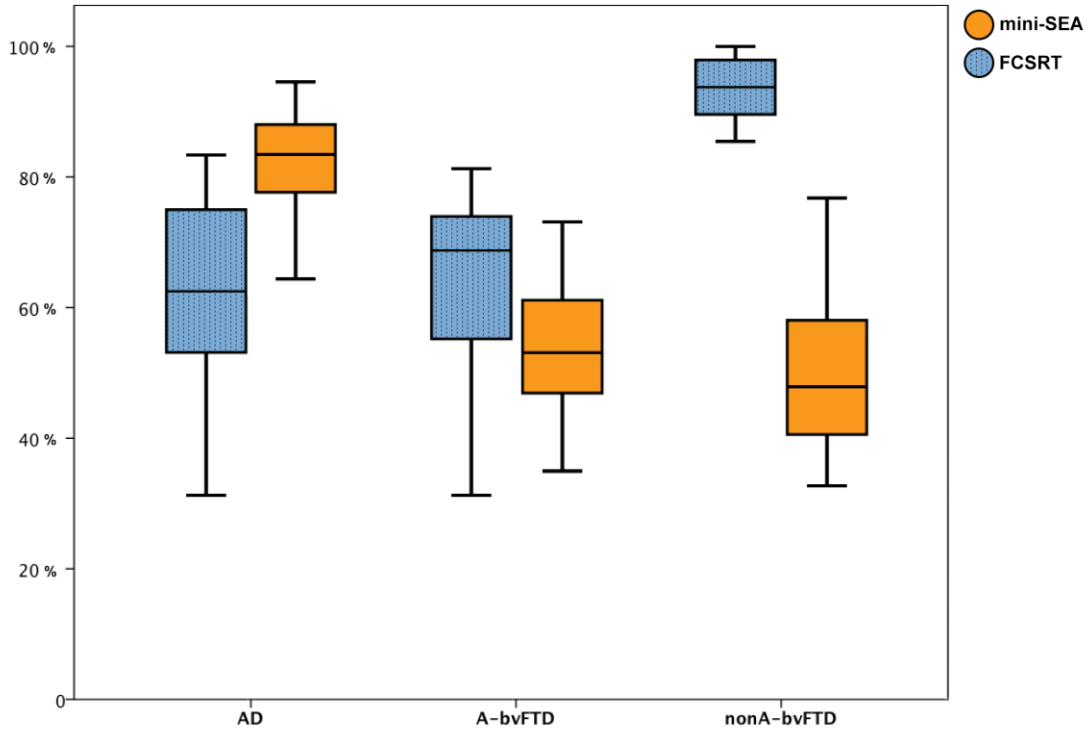

Figure 2

Figures' short titles

Figure 1. Episodic memory & social cognition in bvFTD and Alzheimer's disease.

Figure 2. Episodic memory & social cognition in Alzheimer's disease and in the amnestic and non-amnestic presentation of bvFTD.

Figures' legends

Figure 1. Performance (percentage of correct performance) at the FCSRT and the mini-SEA in Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) (left graph) and ROC curve for the FCSRT and the mini-SEA for the diagnostic distinction between bvFTD and AD.

Figure 2. Performance (percentage of correct performance) at the FCSRT and the mini-SEA in Alzheimer's disease (AD) and amnestic (A-bvFTD) and non-amnestic (nonA-bvFTD) behavioral variant frontotemporal dementia (bvFTD).

Authors' contribution

MB: design, clinical and experimental data acquisition, analysis and interpretation, and manuscript writing.

LCDS: clinical data acquisition, interpretation and manuscript editing.

CO: interpretation and manuscript editing.

AG: interpretation and manuscript editing.

MS: clinical data acquisition and manuscript editing.

BD: clinical and experimental data acquisition and manuscript editing.

MH: design, analysis and interpretation and manuscript writing.

Social cognition deficits – the key to discriminate behavioural variant frontotemporal dementia from Alzheimer's disease regardless of amnesia

Bertoux et al.

Supplementary Material 1

FCSRT scores	AD	bvFTD
Encoding (/16)	13.3 (2.4)	13.6 (2.7)
No. of patients below normative scores	36%	47.4 %
Free recall (/48)	9.8 (5.7) *	15.2 (7.9) §
No. of patients below normative scores	85.7%	65.8%
Total recall (/48)	27.8 (11.3) *	36.9 (11.0) §
No. of patients below normative scores	85.7%	50%
Delayed total recall (/16)	7.9 (4.7) *	12.3 (4.3) §
No. of patients below normative scores	75%	42.1%

Supplementary Table 1 – Episodic memory performance of AD and bvFTD. Mean (SD) Free and Cued Selective Reminding Test (FCSRT) scores and percentage of patients that had pathological scores according to age/education normative scores, for Alzheimer's disease (AD) and behavioural variant frontotemporal dementia (bvFTD).
*Significant difference compared to bvFTD.
§Significant difference compared to AD.

mini-SEA scores	AD	bvFTD	Controls
Total (/ 30)	24.3 (2.9) *	16.3 (3.7) †§	25.8 (1.8) *
Faux-pas (/15)	13.0 (1.7) *	8.7 (2.4) †§	13.2 (1.5) *
Emotion recognition (/15)	11.3 (1.7) *†	7.6 (2.5) †§	12.6 (1.1) *§

Supplementary Table 2 – Social cognition and emotional assessment (mini-SEA) performance of AD, bvFTD and Controls. Mean (SD) mini-SEA total and subscores for Alzheimer's disease (AD), behavioural variant frontotemporal dementia (bvFTD) and Controls.
*Significant difference compared to bvFTD.
†Significant difference compared to Controls.
§Significant difference compared to AD.

Supplementary Material 2

Comparability between bvFTD patients with clinical diagnosis as well as CSF or genetic mutation and bvFTD patients with clinical diagnosis only.

	bvFTD-CLI vs bvFTD-CONF
Mean age at test, y	Z=-.456; p=.651
Education, y	Z=-0.544; p=.601
Disease duration, y	Z=-1.800 p=.080
MMSE (/30)	Z=-1.374; p=.170
FAB (/18)	Z=-.230; p=.821
Executive Neuropsychological scores	
MDRS (/144)	Z=-.748; p=.475
Verbal Fluency (morphologic)	Z=-.464; p=.681
Verbal Fluency (semantic)	Z=-.086; p=.935
mWCST category (/6)	Z=-.875; p=.422
mWCST perseveration errors	Z=-.803; p=.451
mWCST attentional errors	Z=-.181; p=.859
Picture naming (%)	Z=-1.356; p=.183
Digit span forward	Z=-.366; p=.731
Digit span backward	Z=-.157; p=.891

Supplementary Table 3 - Statistical analysis of the differences between patients with a clinical diagnosis of bvFTD without genetic confirmation or pathophysiological biomarkers excluding AD (bvFTD-CLI, n=17) and patients with a clinical diagnosis of bvFTD and a genetic confirmation or pathophysiological biomarkers excluding AD (bvFTD-CONF, n=21).

Demographics, clinical and neuropsychological measures.

For demographics, clinical and neuropsychological measures, no significant differences were observed between bvFTD-CLI and bvFTD-CONF.

FCSRT.

For memory measures (FCSRT), patients were divided into amnestic and non-amnestic groups (using the same procedure as the one described in the main manuscript).

Amnestic patients: there was no difference between amnestic bvFTD-CLI and amnestic bvFTD-CONF on encoding (Z=-0.702 ; p=0.497), free recall (Z=-0.860 ; p=0.400), total recall (Z=-1.068 ; p=.315) and delayed total recall (Z=-0.906 ; p=0.400).

Non-amnestic patients: there was no difference between non-amnestic bvFTD-CLI and non-amnestic bvFTD-CONF on encoding (Z=-0.479 ; p=0.657), free recall (Z=-1.200 ; p=0.238), total recall (Z=-0.083 ; p=.968) and delayed total recall (Z=-0.463 ; p=0.717).

mini-SEA.

Differences between each bvFTD amnestic subgroups were also assessed for the mini-SEA.

Amnestic patients: There was no difference between amnestic bvFTD-CLI and amnestic bvFTD-CONF on the mini-SEA total score (Z=-0.163 ; p=0.905).

Non-amnestic patients: There was no difference between non-amnestic bvFTD-CLI and non-amnestic bvFTD-CONF on the mini-SEA total score (Z=-1.569 ; p=0.129).

Supplementary Material 3

Comparability between amnestic and non-amnestic bvFTD patients, all with clinical diagnosis, without CSF or genetic mutation

	A-bvFTD vs nonA-bvFTD
Mean age at test, y	Z=-.635; p=.536
Education, y	Z=-1.631; p=.148
Disease duration, y	Z=-1.002; p=.388
MMSE (/30)	Z=-1.718; p=.088
FAB (/18)	Z=-1.668; p=.109
Executive Neuropsychological scores	
MDRS (/144)	Z=-1.451; p=.181
Verbal Fluency (morphologic)	Z=-1.532; p=.181
Verbal Fluency (semantic)	Z=-1.457; p=.174
mWCST category (/6)	Z=-1.785; p=.091
mWCST perseveration errors	Z=-.757; p=.470
mWCST attentional errors	Z=-.646; p=.534
Picture naming (%)	Z=-1.664; p=.203
Digit span forward	Z=-1.549; p=.142
Digit span backward	Z=-1.521; p=.152

Supplementary Table 4 - Statistical analysis of the differences between A-bvFTD (n=10) and nonA-bvFTD (n=7) patients, all with clinical diagnosis without genetic confirmation or pathophysiological biomarkers excluding AD.

	A-bvFTD vs nonA-bvFTD
Mean age at test, y	Z=-.498; p=.651
Education, y	Z=-1.582; p=.129
Disease duration, y	Z=-.829; p=.427
MMSE (/30)	Z=.000; p=1.000
FAB (/18)	Z=-.153; p=.882
Executive Neuropsychological scores	
MDRS (/144)	Z=-.888; p=.384
Verbal Fluency (morphologic)	Z=-1.356; p=.182
Verbal Fluency (semantic)	Z=-1.149; p=.278
mWCST category (/6)	Z=-.704; p=.503
mWCST perseveration errors	Z=-.124; p=.904
mWCST attentional errors	Z=-.307; p=.808
Picture naming (%)	Z=-1.406; p=.143
Digit span forward	Z=-.348; p=.780
Digit span backward	Z=-.475; p=.661

Supplementary Table 5 - Statistical analysis of the differences between A-bvFTD (n=9) and nonA-bvFTD (n=12) patients, all with genetic confirmation or pathophysiological biomarkers excluding AD.

Demographics, clinical and neuropsychological measures.

For demographics, clinical and neuropsychological measures, no significant differences were observed between A-bvFTD and nonA-bvFTD in bvFTD-CLI only (Table A.4) and in bvFTD-CONF only (Table A.5).

FCSRT.

For memory measures (FCSRT), patients were divided into amnestic and non-amnestic groups (using the same procedure as the one described in the main manuscript).

bvFTD-CLI: there was a significant difference between amnestic bvFTD-CLI and non-amnestic bvFTD-CLI on encoding (Z=-2.187 ; p=0.034), free recall (Z=-1.991 ; p=0.049), total recall (Z=-3.849 ; p=.000001) and delayed total recall (Z=-3.801 ; p=0. 000001).

bvFTD-CONF: there was a significant difference between amnestic bvFTD-CONF and non-amnestic bvFTD-CONF on encoding (Z=-2.728 ; p=0.005), free recall (Z=-3.320 ; p=0.0005), total recall (Z=-3.420 ; p=.00001) and delayed total recall (Z=-3.379 ; p=0.0002).

mini-SEA.

Differences between each bvFTD diagnosis subgroups were also assessed for the mini-SEA.

bvFTD-CLI: There was no difference between amnestic bvFTD-CLI and non-amnestic bvFTD-CLI on the mini-SEA total score (Z=-0.640 ; p=0.554).

bvFTD-CONF There was no difference between non-amnestic bvFTD-CONF and non-amnestic bvFTD-CONF on the mini-SEA total score (Z=-0.683 ; p=0.536).

Supplementary Material 4

Comparability between AD patients with clinical diagnosis as well as CSF and AD patients with clinical diagnosis only.

	AD-CLI vs AD-CONF
Mean age at test, y	Z=-1.906; p=.059
Education, y	Z=-.565; p=.614
Disease duration, y	Z=-.327 p=.755
MMSE (/30)	Z=-.025; p=.981
FAB (/18)	Z=-1.357; p=.198
Executive Neuropsychological scores	
Verbal Fluency (morphologic)	Z=-.579; p=.631
Verbal Fluency (semantic)	Z=-1.052; p=.317
Picture naming (%)	Z=-.407; p=.727
Digit span forward	Z=-1.806; p=.076
Digit span backward	Z=-1.875; p=.061

Supplementary Table 6 - Statistical analysis of the differences between patients with a clinical diagnosis of AD without pathophysiological biomarkers of AD (AD-CLI n=15) and patients with a clinical diagnosis of AD and pathophysiological biomarkers of AD (AD-CONF, n=13).

For demographics, clinical and neuropsychological measures, no significant differences were observed between AD-CLI and AD-CONF (Table A.6).

FCSRT.

AD-CLI vs AD-CONF: there was no significant difference between AD-CLI and AD-CONF on encoding (Z=-.450 ; p=0.667), free recall (Z=-.905 ; p=0.373), total recall (Z=-.587 ; p=.581) and delayed total recall (Z=-.591 ; p=0.581).

mini-SEA.

AD-CLI vs AD-CONF: there was no significant difference between AD-CLI and AD-CONF on the mini-SEA score (Z=-.342; p=0.755).

Supplementary Material 5

Correlations analyses between mini-SEA subtests and FCSRT subscores in bvFTD and AD.

Correlations[a]

			FCSRT_ENC	FCSRT_FR	FCSRT_TR	FCSRT_DRT	SEA	ToM	Emot
Spearman's rho	FCSRT_ENC	Correlation Coefficient	1,000	,600**	,572**	,494**	,204	,128	,286
		Sig. (2-tailed)	.	,000	,000	,002	,219	,451	,087
		N	38	38	38	38	38	37	37
	FCSRT_FR	Correlation Coefficient	,600**	1,000	,806**	,719**	,175	-,084	,414*
		Sig. (2-tailed)	,000	.	,000	,000	,293	,623	,011
		N	38	38	38	38	38	37	37
	FCSRT_TR	Correlation Coefficient	,572**	,806**	1,000	,859**	,062	-,227	,369*
		Sig. (2-tailed)	,000	,000	.	,000	,713	,176	,024
		N	38	38	38	38	38	37	37
	FCSRT_DRT	Correlation Coefficient	,494**	,719**	,859**	1,000	,087	-,172	,308
		Sig. (2-tailed)	,002	,000	,000	.	,603	,310	,063
		N	38	38	38	38	38	37	37
	SEA	Correlation Coefficient	,204	,175	,062	,087	1,000	,782**	,733**
		Sig. (2-tailed)	,219	,293	,713	,603	.	,000	,000
		N	38	38	38	38	38	37	37
	ToM	Correlation Coefficient	,128	-,084	-,227	-,172	,782**	1,000	,197
		Sig. (2-tailed)	,451	,623	,176	,310	,000	.	,241
		N	37	37	37	37	37	37	37
	Emot	Correlation Coefficient	,286	,414*	,369*	,308	,733**	,197	1,000
		Sig. (2-tailed)	,087	,011	,024	,063	,000	,241	.
		N	37	37	37	37	37	37	37

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. DIAG = 1,00

Supplementary Table 7 - Statistical analysis of the correlations between mini-SEA (SEA) scores (ToM, Emot) and FCSRT scores (ENC, FR, TR & DRT) in bvFTD patients. Corrected threshold of significance is p=0.007. FCSRT_ENC=Encoding score; FCSRT_FR=Free Recall score; FCSRT_TR=Total Recall score; FCSRT_DTR=Delayed Total Recall score; SEA=mini-Social cognition and emotional Assessment total score; TOM=Faux-pas test score; EMOT=Emotion recognition score

Correlations[a]

			FCSRT_ENC	FCSRT_FR	FCSRT_TR	FCSRT_DRT	SEA	ToM	Emot
Spearman's rho	FCSRT_ENC	Correlation Coefficient	1,000	,170	,211	,140	,049	,164	-,093
		Sig. (2-tailed)	.	,407	,301	,496	,811	,424	,650
		N	26	26	26	26	26	26	26
	FCSRT_FR	Correlation Coefficient	,170	1,000	,459*	,461*	-,345	-,271	-,308
		Sig. (2-tailed)	,407	.	,016	,016	,078	,172	,118
		N	26	27	27	27	27	27	27
	FCSRT_TR	Correlation Coefficient	,211	,459*	1,000	,782**	-,296	-,217	-,244
		Sig. (2-tailed)	,301	,016	.	,000	,135	,276	,221
		N	26	27	27	27	27	27	27
	FCSRT_DRT	Correlation Coefficient	,140	,461*	,782**	1,000	-,229	-,096	-,236
		Sig. (2-tailed)	,496	,016	,000	.	,250	,634	,235
		N	26	27	27	27	27	27	27
	SEA	Correlation Coefficient	,049	-,345	-,296	-,229	1,000	,806**	,821**
		Sig. (2-tailed)	,811	,078	,135	,250	.	,000	,000
		N	26	27	27	27	27	27	27
	ToM	Correlation Coefficient	,164	-,271	-,217	-,096	,806**	1,000	,403*
		Sig. (2-tailed)	,424	,172	,276	,634	,000	.	,037
		N	26	27	27	27	27	27	27
	Emot	Correlation Coefficient	-,093	-,308	-,244	-,236	,821**	,403*	1,000
		Sig. (2-tailed)	,650	,118	,221	,235	,000	,037	.
		N	26	27	27	27	27	27	27

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

a. DIAG = 2,00

Supplementary Table 8 - Statistical analysis of the correlations between mini-SEA (SEA) scores (ToM, Emot) and FCSRT scores (ENC, FR, TR & DRT) in AD patients. Corrected threshold of significance is p=0.007. FCSRT_ENC=Encoding score; FCSRT_FR=Free Recall score; FCSRT_TR=Total Recall score; FCSRT_DTR=Delayed Total Recall score; SEA=mini-Social cognition and emotional Assessment total score; TOM=Faux-pas test score; EMOT=Emotion recognition score

Supplementary Material 6

We replicated the logistic regression analyses using independent random samples from the initial dataset, a method somewhat similar to jack-knife cross-validation, which was not directly feasible with SPSS.

At first, observations were randomly selected by SPSS at a specified level (we chose to automatically set the selection on approx. 30%, 50% then 75% of patients), creating a filter variable. The logistic regression analyses were then performed again only through the filter variable. Importantly, the samples were randomly selected for each of the three comparisons (bvFTD vs AD; A-bvFTD vs AD; nonA-bvFTD vs AD).

bvFTD vs AD	**FCSRT (Total recall)**	**Mini-SEA (Total)**
Sample 1 – 15% of observations	60.0%	86.7%
Sample 2 – 30% of observations	68.4%	83.3%
Sample 3 – 50% of observations	62.2%	91.9%
Sample 4 – 75% of observations	58.7%	91.9%

A-bvFTD vs AD	**FCSRT (Total recall)**	**Mini-SEA (Total)**
Sample 1 – 15% of observations	70.0% *	80.0%
Sample 2 – 30% of observations	50.0% *	80.0%
Sample 3 – 50% of observations	62.5% *	79.2%
Sample 4 – 75% of observations	57.1% *	82.9%

nonA-bvFTD vs AD	**FCSRT (Total recall)**	**Mini-SEA (Total)**
Sample 1 – 15% of observations	100% *	90.0%
Sample 2 – 30% of observations	100% *	83.3%
Sample 3 – 50% of observations	100% *	84.2%
Sample 4 – 75% of observations	100% *	85.7%

* As both the Total recall score of the FCSRT was used to split the group into A-bvFTD and nonA-bvFTD, there analyses are circular.

Taken together, this last analysis confirm our sample-based results, showing that the mini-SEA is more accurate (from 83.3% to 91.9%) than the FCSRT (from 58.7% to 68.4%) to distinguish bvFTD from AD at presentation. For the mini-SEA, similar results were observed when contrasting A-bvFTD (from 79.2% to 82.2%) or nonA-bvFTD to AD (from 83.3% to 90.0%).