So Close Yet So Far: Executive Contribution to Memory Processing in Behavioral Variant Frontotemporal Dementia

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Abstract

Background: Memory impairment in behavioral variant frontotemporal dementia (bvFTD) is traditionally considered to be mild and attributed to prefrontal cortex dysfunction. Recent studies, however, indicated that some patients can present with a memory impairment of the hippocampal type, showing storage and consolidation deficits in addition to the more executive/prefrontal related encoding and strategic difficulties.

Objective: This study aimed to study the relationship between executive functions (EF) and memory processes in bvFTD via a data-driven approach.

Method: Participants consisted of 71 bvFTD (among which 60.6% had a lumbar puncture showing non-Alzheimer biomarker profile) and 60 controls (among which 45% had amyloid imaging showing a normal profile). EF were assessed by the Frontal Assessment Battery, semantic/lexical verbal fluency tests, and forward/backward digit spans. Patients were split into amnestic (n = 33) and non-amnestic (n = 38) subgroups based on normative data (total recall score) from the Free and Cued Selective Reminding Test (FCSRT). Relationships between FCSRT subscores and EF measures were explored through hierarchical clustering analysis, partial correlation analysis with an EF component, and automated linear modeling.

Results: Convergent findings across the statistical approaches show that, overall, memory performance was independent from EF in bvFTD whereas the relationship was stronger in controls. Indeed, in bvFTD, memory performance did not cluster with EF, was not correlated with the EF component, and was only partially (4%–12.7%) predicted by EF.

Discussion: These findings show that executive dysfunctions cannot solely explain the memory deficits occurring in bvFTD. Indeed, some patients present with a genuine amnesia affecting storage and consolidation abilities, which are independent from executive dysfunctions. On the clinical level, this study highlights the importance of revising the neuropsychological diagnosis criteria for bvFTD.

Keywords: Consolidation, encoding, episodic amnesia, executive functions, Free and Cued Selective Reminding Test, frontotemporal dementia, memory, retrieval, storage

Introduction

Clinical distinction of behavioral-variant frontotemporal dementia (bvFTD) from Alzheimer's disease (AD) has historically relied on a dichotomous view of cognitive symptoms in these syndromes. While the presence of an episodic amnestic syndrome is required for the diagnosis of AD [1], diagnostic criteria for bvFTD describes a dysexecutive cognitive profile, with relative sparing of memory functions [2]. There is, however, an ongoing debate in the literature on the usefulness of these two respective criteria in the differential diagnosis of bvFTD and AD [3, 4]. Indeed, an increasing number of studies have shown that some typical AD patients can present with severe executive dysfunction [5–7] and some bvFTD patients can present with severe amnesia [8, 9], including pathologically confirmed cases [10–12]. Similarly, at the pathological level significant pre-frontal and hippocampal atrophy can be observed in AD and bvFTD, respectively [5, 11, 13].

Importantly, however, executive function and memory are not independent from each other and there is substantial evidence that executive dysfunction can impact on memory performance, even when medial temporal lobe areas are relatively spared [14]. Thus, memory impairment in bvFTD patients has previously been considered to be secondary to significant prefrontal cortex (PFC) dysfunction in these patients. The contribution of prefrontal regions in episodic memory processing is well established [15, 16] and patients with PFC lesions typically exhibit impaired performance in neuropsychological memory tests, with deficits in free recall, source memory, memory for temporal order, recency, frequency, and associative learning (for a review, see [17]). In more detail, poor organization of information and lack of efficient learning strategies have been suggested to explain encoding difficulties of PFC patients, whereas their low retrieval performance has been attributed to an inability to implement effective retrieval strategies [17, 18]. Finally, PFC patients often lack of insight into their own memory difficulties and fail to spontaneously use compensatory strategies, akin to bvFTD [19].

One approach to delineate the contribution of executive/PFC mechanisms and memory/hippocampal processes is to use memory tests that separate each step of the learning, storage, and retrieval procedures. The Free and Cued Selective Reminding Test (FCSRT; [20]) was designed specifically for this purpose, as it uses semantic cueing for controlling effective encoding and facilitating subsequent cued recall of words, for those items that are not spontaneously retrieved. This procedure allows clinicians to identify deficits in specific steps of learning or retrieval, including associative encoding, free recall, cued recall, recognition, delayed free and cued recall. In particular, the performance in cued recall and delayed cued recall is assumed to provide a 'purer' measure of memory storage and consolidation (and thus tapping into hippocampal functioning), while encoding and free recall are supposed to rely more on executive/prefrontal functioning.

Previous studies using the FCSRT in bvFTD have reported encoding and retrieval strategy difficulties [21, 22], suggesting that executive dysfunction impacts on memory performance

in these patients. More importantly, however, when performance on cued recall and delayed recall were also considered, bvFTD patients, although outperforming AD in both studies, presented evidence of a "genuine memory deficit" [21]. These findings suggested that bvFTD patients may show significant memory storage and consolidation deficits, in addition to encoding and strategic retrieval difficulties. Studies using different neuropsychological memory tests have not replicated these results, instead supporting the notion that executive/prefrontal dysfunctions should be considered the main predictor of memory impairment in bvFTD [23, 24]. One possible explanation for this discrepancy is that only a proportion of bvFTD patients show "true amnesia" [11]. Indeed, a bi-modal distribution of FCSRT performance has been observed in bvFTD patients, with approximately 50% of patients presenting with storage and consolidation deficits, while the other half showed impairments in encoding and retrieval strategy [9].

To our knowledge, no previous study has attempted to delineate executive and memory dysfunction in amnestic versus non-amnestic bvFTD. The current study is aimed at addressing this issue by taking a data-driven approach to investigate the relationship between executive task performance and memory scores from the FCSRT in a large group of bvFTD patients, the majority of which had biomarker data to support their diagnoses. To explore the impact of executive dysfunction on memory performance, bvFTD patients were split into amnestic versus non-amnestic subgroups and contrasted to age-matched healthy controls.

Materials and Methods

Participants

A total of 180 participants were included in this study. We included bvFTD patients with memory
impairment if other core diagnostic criteria were present [2]. All bvFTD patients were selected from the database of the Memory and Alzheimer Institute of the Pitie´-Salpeˆtrie`re Hospital (IM2A Paris, France). All patients underwent extensive neuropsychological assessment as well as T1-MRI (and/or SPECT imaging). From an initial sample of 111 patients, we retained 71 bvFTD patients. A total of 39 patients were excluded from the study because of missing cognitive data, concomitant motor-neuron disease, vascular lesions, or alcoholism (n = 17); atypical clinical and imaging evolution compatible with the diagnosis of non-progressive bvFTD—or phenocopy (n = 12); the presence of an AD biomarker profile as revealed by CSF analyses following a lumbar puncture (n = 8); atypical evolution not in accordance with initial diagnosis (i.e., clinical and cognitive improvement, n = 2). One last patient was excluded because French was not his native language. Of these 71 patients who received a clinical diagnosis of bvFTD on the basis of clinical, cognitive and imaging examinations, 60.6% (n = 43) had additional diagnosis confirmation either through normal cerebrospinal fluid (CSF) measures of phospho-tau, total-tau, and amyloid-þ levels (n = 28), or through positive genetic testing (n = 15).

From an initial sample of 69 participants, we retained 60 controls. They were volunteers recruited through the Biomage (ANR-07-LVIE-002-01) and Imabio3 studies (PHRC 2010) in France (n = 27) or through the Cognitive Neurology and Dementia Unit, Hospital del

Salvador, University of Chile (n = 33). Among the original sample (n = 69), 100% underwent a neuropsychological examination and a T1 MRI and 43.5% (n = 30) underwent 11C-PiB-PET imaging. On the basis of these examinations, we excluded 6 controls with abnormal atrophy of the brain or significant vascular signs and 3 controls with positive amyloid imaging (global 11C-PiB >1.4). Among the controls who underwent the amyloid imaging, all other participants had a negative amyloid imaging defined by a global 11C-PiB retention lower than 1.4. No differences were observed on age, education, and screening (Frontal Assessment Battery (FAB) and Mini-Mental State Examination) measures between French and Chilean controls.

Biological and clinical data of patients were collected during the routine clinical workup and were retrospectively extracted for the purpose of this work. The ethics and scientific committees of the East Metropolitan Health Service, Chile University (Chile) and Pitié-Salpêtrière hospital (France) approved the recruitment and testing of controls and all provided written informed consent.

Assessment of memory

All participants underwent the FCSRT, a memory test based on a semantic cueing method that controls for effective encoding of 16 words and facilitates retrieval by semantic cueing. Immediate cued recall was tested in a first phase to control for encoding (Encoding score). Then, the memory phase was performed in three successive trials. Each trial included a free recall attempt consisting of spontaneous recall of as many items as possible, then a cued recall attempt using an aurally presented semantic category for items that were not spontaneously retrieved by the patients. The same semantic cue given during the initial encoding stage was used. This provided a free recall score and a cued recall score (maximum score = 48). We computed a percentage of sensitivity to cues (free recall score – total recall score)/(total recall score – 48). Following a delay of 30 min, a final recall trial was performed, providing free and cued delayed recall scores (maximum score = 16). Based on cut-offs recommended by normative data for the FCSRT (total recall score), bvFTD patients were divided into subgroups of patients presenting with an 'amnesic' profile (n = 33, amnestic-bvFTD) and a 'non-amnesic' profile (n = 38, nonAmnestic-bvFTD), in line with previously reported procedures [25].

Assessment of executive functioning

The FAB [26] and phonemic and category fluency tests as well as forward and backward digit spans were administered to all participants.

Statistical analyses

Statistical analyses were conducted with IBM SPSS 20. Demographic and clinical variables were analyzed using Mann-Whitney test and ANOVAs. All cognitive variables were then standardized (transformed to z-scores) based on data from the control group's performance.

To determine how closely EF and memory sub-processes were related, we used a two-step approach. As a first step, hierarchical cluster analysis using Ward's method was used to determine how closely EF and memory sub-processes were related. Briefly, the cluster analysis defines each variable as an individual cluster; clusters are then sequentially merged as per their squared Euclidean distance in a geometric space where the number of variables set the number of dimensions. The clusters extracted from the optimal model are then plotted on a dendrogram representing the relationships of similarity among the group of variables. As a second step, a principal component analysis was conducted only on EF measures, in order to extract a single component of executive functioning. Correlations (Spearman's rank coefficient) between this EF factor and the memory scores were then analyzed with age as a nuisance variable.

Finally, to determine which specific measures of EF significantly impact memory performance and to what extent, an automatic linear modeling analysis was employed.

Results

Group comparisons

Demographic and cognitive scores are presented in Table 1 and Fig. 1, as well as significant differences observed in the ANOVA or in post hoc comparisons between groups. No differences on age and education were observed. Disease duration and Mini-Mental State Examination scores did not differ across patients' subgroups. Controls outperformed patients on all cognitive measures. Patients did not differ on digit spans and FAB scores, but amnestic-bvFTD patients obtained lower fluency scores than nonAmnestic-bvFTD patients. Results were identical after controlling for age.

First step: Relationship between EF and memory processes

Hierarchical clustering architecture

Results from the hierarchical cluster analysis are shown on Fig. 2. On these dendrograms, similar variables were joined at earlier stages (bottom of each dendrogram), whereas those which were less similar were joined at later stages of the analysis (at the top). In the amnestic-bvFTD group (Fig. 2A), four distinct clusters were identified: an attention/working-memory cluster composed from digit spans forward and backward, a pure EF cluster composed from FAB and semantic and lexical fluency, and two pure memory clusters, one composed from encoding, free recall and delayed free recall and finally, one composed from cued and delayed cued recall and recognition. In the nonAmnestic-bvFTD group (Fig. 2B), five clusters were identified: a pure EF cluster with FAB and fluency, an attention/working-memory cluster with digit spans forward and backward, a pure memory cluster with encoding, free and delayed free recalls, another memory cluster composed from cued recall and recognition, and an isolated delayed cued recall cluster. In the control group (Fig. 2C), one pure memory cluster was identified (composed from cued and delayed cued recalls), a pure executive cluster (span and fluency), an isolated recognition cluster and a mixed cluster with encoding, free and delayed free recalls as well as FAB.

Correlations with the EF component

In the amnestic-bvFTD group, no significant correlations were observed between the EF component extracted from the principal component analysis and the memory scores. In non-amnestic patients, encoding was significantly correlated with the EF component ($R = 0.50$, $p < 0.05$). In controls, free recall, total (free+cued) recall, total (free+cued) delayed recall, and sensitivity to cueing were significantly correlated with the EF component (respectively $R = 0.27$; $R = 0.58$; $R = 0.32$; and $R = 0.52$ all $p < 0.05$). Results were similar when including age as a nuisance covariate.

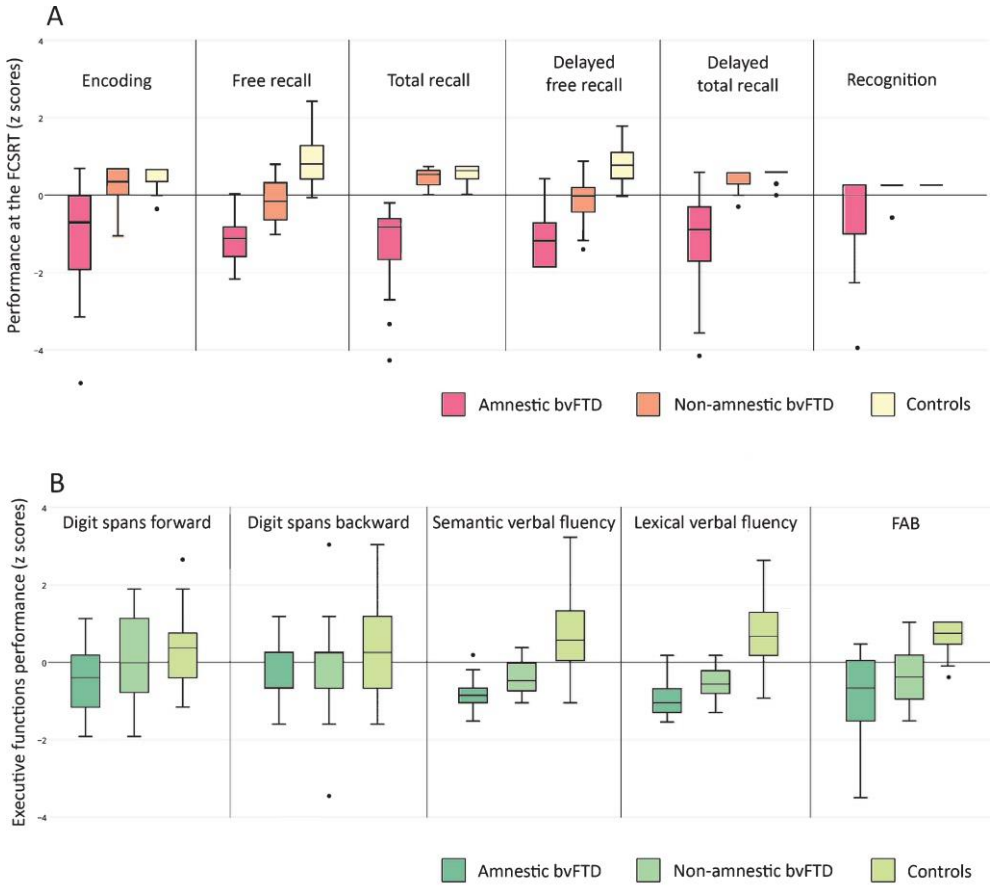

Fig. 1. Performance (z-scores) of amnestic bvFTD, non-amnestic bvFTD and controls at (A) the Free and Cued Selective Reminding Test (FCSRT) for encoding, free recall, total recall, delayed free recall, delayed total recall and recognition subscores and (B) at the digit span forward & backward, semantic, and lexical verbal fluency and Frontal Assessment Battery (FAB)

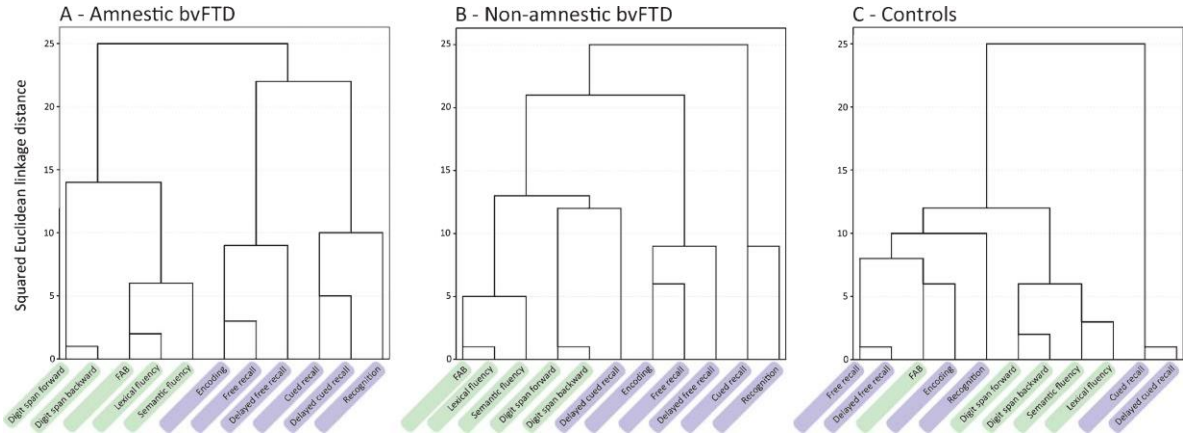

Fig. 2. Dendrogram using Ward's linkage, showing the hierarchical cluster architecture of memory and executive scores for (A) amnestic bvFTD, (B) non-amnestic bvFTD and (C) controls. Green variables represent executive function measures and blue variables represent Free and Cued Selective Reminding Test (FCSRT) subscores. FAB, Frontal Assessment Battery.

Table 1

Demographics and neuropsychological tests differences between groups

	Amnestic bvFTD (n = 33)	NonAmnestic bvFTD (n = 38)	Controls (n = 60)	Differences <0.01
Demographics and screening test				
Age (years)	64.89 (13.71)	66.74 (9.35)	68.78 (7.05)	N.S.
Education (years)	11.15 (3.66)	11.67 (3.77)	12.81 (3.04)	N.S.
Disease duration (years)	3.41 (2.03)	3.27 (2.27)	–	N.S.
MMSE (/30)	24.42 (3.97)	23.03 (3.82)	29.22 (0.93)	*, b, c
Executive functioning				
Digit span forward	4.78 (0.94)	5.64 (1.47)	5.82 (1.25)	*
Digit span backward	3.07 (0.73)	3.68 (1.25)	4.07 (0.99)	*, b
FAB (/18)	11.10 (3.60)	13.20 (2.91)	16.95 (1.17)	*, b, c
Lexical fluency	4.90 (3.66)	7.47 (3.76)	19.00 (6.10)	*, a, b, c
Semantic fluency	9.03 (4.01)	13.31 (4.37)	25.37 (10.14)	*, a, b, c
Memory processes (FCSRT)				
Encoding (/16)	10.84 (3.84)	14.57 (1.73)	15.42 (0.78)	*, a, b
Free recall (/48)	10.12 (6.20)	20.32 (5.84)	31.36 (5.52)	*, a, b, c
Cued recall (/48)	17.45 (7.57)	23.84 (4.85)	15.05 (5.06)	*, a, b, c
Total recall (/48)	27.58 (9.94)	44.16 (3.17)	46.41 (1.85)	*, a, b, c
Sensitivity to cues (%)	47.21 (18.83)	86.78 (9.94)	90.76 (11.11)	*, a, b
Delayed free recall (/16)	2.54 (2.19)	7.00 (2.66)	11.71 (2.22)	*, a, b, c
Delayed cued recall (/16)	6.61 (3.11)	8.06 (1.93)	4.02 (2.11)	*, b, c
Delayed total recall (/16)	9.43 (4.06)	15.06 (1.37)	15.73 (0.52)	*, a, b
Recognition (/16)	14.89 (1.49)	15.62 (1.72)	16 (0)	*, a, b, c

Maximum test scores (where applicable) indicated in brackets; Mean (Standard deviation). N.S., non-significant; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; FCSRT, Free and Cued Selective Reminding Test. $^{*}p < 0.01$ for ANOVA; $^{a}p < 0.01$ between bvFTD subgroups; $^{b}p < 0.01$ between Controls and amnestic patients; $^{c}p < 0.01$ between controls and non-amnestic patients.

Second step: Influence of EF measures on bvFTD's memory performance

Automatic linear modeling

In order to explore which EF measure could influence the memory performance in bvFTD, all EF measures were entered in an automatic linear model as predictor variables and each memory score was sequentially considered as the target variable. This analysis was run in both bvFTD subgroups. In amnestic-bvFTD, the results showed that the only memory score to be significantly ($p < 0.05$) predicted by EF performance was free recall, but to a minor extent (12.7% of its variance was predicted by semantic fluency performance). EF also appeared to influence encoding and total recall performances (respectively predicting 4.5% and 4.6% of variance), but this link was non significant. EF did not influence any of the remaining processes (namely free and total delayed recalls, recognition and sensitivity to cues). In non-amnestic bvFTD, no significant effect of EF

performance on memory processing was observed. Although EF influenced encoding, free 4.3%, 4.3% and 6.8% of their variance), this failed to reach statistical significance.

Discussion

These data-driven results clearly show that, in bvFTD, memory processes were overall independent from executive functioning regardless of the amnestic presentation of the disease. First, the clustering approach shows how memory scores were distinct from executive measures in both amnestic and non-amnestic presentation of bvFTD. By contrast, this relationship between EF and memory was stronger in controls, as the FAB clustered with encoding as well as free and delayed recall. In line with this result, the correlation analysis showed that, while the EF component extracted from the principal component analysis was not correlated with any of the memory scores in amnestic-bvFTD, it was correlated with encoding performance in non-amnestic patients and with free recall, total recall, sensitivity to cueing, and free delayed recall scores in controls. Taken together, these results suggest that memory performance in bvFTD is largely independent from executive functioning, while it is correlated with EF in healthy elderly controls. This indicates that memory and executive function in bvFTD might be more independent than previously thought and that the episodic amnesia observed in amnestic-bvFTD cannot be solely explained by an impairment of executive/prefrontal functions alone.

In a second step, we investigated the specific contribution of EF measures on memory performance in bvFTD through an automated linear modelling approach. By contrast to the clustering and correlation analyses, this approach considered each memory score independently from the others, allowing a more specific investigation of which EF score contributed to which memory process. We observed that in both amnestic and non-amnestic subgroups of bvFTD, the influence of EF was negligible. In sum, converging evidences from the different statistical approaches showed that the contribution of EF on memory processes is not only weaker that what was assumed in bvFTD, but also qualitatively different from what was expected.

Numerous studies have demonstrated that pre-frontal cortex is critical in various aspects of episodic memory, such as encoding and retrieval [15, 17, 18, 27, 28]. In more detail, it has been suggested that PFC dysfunction disrupts the executive processes involved in voluntary encoding and retrieval processes and particularly in the organization of information necessary for an optimal encoding as well as the use and monitoring of efficient retrieval strategies needed to recall these information [28]. This view is shared by many authors who consider executive/prefrontal processes as critically involved in memory processing [29, 30]. Historically, these conceptions explain why the memory deficits observed in bvFTD were exclusively attributed to executive/prefrontal dysfunctions [23, 24, 31]. Prefrontal atrophy is indeed characteristic of bvFTD [32] and damage to this particular region has been related to core symptoms of bvFTD, such as behavioral dysfunction, social cognition deficit or executive impairment [19, 33, 34]. In addition, several studies have observed significant relationship between PFC atrophy and memory performance in bvFTD [5, 35], although so far, no study explored this link using tests that target the specific processes of episodic memory. The contribution of other episodic memory structures has also to be investigated in bvFTD. Indeed, in bvFTD, significant postmortem pathology occurs in the

hippocampus, even in patients dying early during the course of the disease [36, 37] and recent in vivo investigations have shown that atrophy of the hippocampus could be as severe in bvFTD than it is in AD [11, 13]. Furthermore, one neuropsychological investigation of memory performance in bvFTD with biological evidence of the diagnosis has shown that memory storage and consolidation processes—that are hippocampus-mediated processes—could also be impaired in bvFTD [9]. Taken together with a previous study having highlighted the correlation between episodic memory deficit and hippocampal degeneration in bvFTD [38], this highlight a broader involvement of atrophy within the brain, thus including other regions such as the hippocampus.

In line with these results, we believe that our findings in amnestic and non-amnestic subgroups of bvFTD reflect different PFC and hippocampal integrity. While both amnestic and non-amnestic patients presented with executive dysfunction characteristic of a PFC involvement, only the memory profile of amnestic-bvFTD patients revealed a typical pattern of hippocampal atrophy, with storage and consolidation deficit [39, 40]. Consecutively, it may explain why the relationship between EF impairment and encoding difficulties is closer in non-amnestic patients than it is in amnestic patients. Indeed, EF impairment and encoding deficits may rely on the same PFC involvement in non-amnestic patients. By contrast, this relationship is weak in amnestic patients as EF and memory deficit are related to the involvement of different brain regions, respectively the PFC and the hippocampus. By extension, the stronger relationship between EF and memory in controls may reveal a stronger dependency of memory processing on EF, which support strategic aspects of episodic memory. It may also reflect the subtle and normal age-related cognitive decline affecting both executive and memory functioning [41–44] as well as prefrontal and hippocampal age-related grey mater loss (for a review, see [45]). Taken together, this different normal and pathological neural involvement would explain why the contribution of EF seems to decrease as a function of amnestic impairment, as it seems more important in controls than in non-amnestic patients and more important in non-amnestic patients than in amnestic patients. In sum, the results of the present study highlight that EF involvement has only a negligible influence on the memory impairments observed in bvFTD, in contrary to what was previously thought. These results also show that bvFTD patients could suffer from a genuine amnesia characterized by a deficit in memory storage and consolidation that could not be explained by EF deficits or PFC involvement but are more likely to be attributed to the hippocampus degeneration that could be observed in this disease.

This study has clear clinical implications. At present, the relative preservation of episodic memory and the presence of executive dysfunctions are among the diagnostic criteria of bvFTD [2]. Thus, not only the episodic amnesia in bvFTD is underestimated but it is also presumed to be predominantly explained by executive dysfunction. Our finding contradict this idea by showing that, in a bvFTD population where the majority of patients have biomarkers supporting the diagnosis, EF has only a little influence on memory performance, in both amnestic and non-amnestic form of the disease. These findings also suggest that, although the FCSRT was proposed as a useful clinical diagnostic tool to objectively assess the presence of an episodic amnesia in AD [46], caution should be observed when interpreting results for the purpose of differential diagnosis for bvFTD. This

highlights the importance of a diagnosis relying on a clinical-biological entity supported by the evidence of positive pathophysiological biomarker. However, as such examination are not always possible, one possibility is that the FCSRT can be used alongside tests of social cognition (like the mini-Social cognition & Emotional Assessment) that have been shown to reliably distinguish bvFTD from AD regardless of amnestic presentation of bvFTD [25]. Another neuropsychological way of distinguishing bvFTD from AD is the use of spatial navigation tests, which have been found to be specifically impaired in AD [49].

This study is to date, the first data-driven investigation of the relationship between EF and memory processes bvFTD by taking the level of amnesia into account. Despite describing this relationship through converging statistical evidence on large groups of bvFTD patients and controls, our approach was limited by the range of the neuropsychological tests that we used. Similarly, in this study, we clubbed phonemic and category fluency under executive measures; even though these tests rely on executive processes, they also rely heavily on other non-executive cog- studies should use a larger range of EF measures to extend our findings, especially in including neuropsychological EF tests that tap into PFC subregions that may not be measured by the tests that we used, such as the ventral parts of the PFC. As an example, the Hayling test which taps into more ventral lateral and medial PFC regions [33, 47] could be particularly interesting to relate to memory processes as these PFC regions have been also shown to be involved in episodic encoding and semantic retrieval [48]. Finally, future investigations of the FCSRT would benefit from incorporating structural or functional neuroimaging to clarify the neural mechanisms underlying memory performance in bvFTD. Despite these shortcomings, the results should further improve the diagnostics and disease management of bvFTD.

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