# Does amnesia specifically predict Alzheimer's pathology? A neuropathological study

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**Highlights**

- Amnesia is traditionally considered as the key clinical symptom of AD;
- A third of patients with AD pathology were non-amnesic at presentation;
- Almost half of patients without AD pathology were amnesic at presentation;
- Memory performance has a poor accuracy to predict AD pathology;

**Abstract**

Amnesia is a key component of Alzheimer's disease (AD) and the most important feature of its clinical diagnosis but its specificity has recently been challenged. This study investigated the ability of amnesia to predict AD in a clinicopathological dementia series. Ninety-one patients to which free and cued verbal memory assessment was administered during early cognitive decline, were followed until autopsy. Patients' histological diagnoses were classified as pure-AD, mixed-AD and non-AD pathologies. Data-driven automated classification procedures explored the correspondence between memory performance and pathological diagnoses. Classifications revealed three clusters of performance reflecting different levels of amnesia. Little correspondence between these clusters and the presence of AD pathology was retrieved. A third of patients with pure/mixed AD pathology were non-amnesic at presentation and ≈45% of patients without AD pathology were amnesic. Data-driven prediction of AD pathology based on memory also had a poor accuracy. Free and cued memory assessments are fair tools to diagnose an amnesic syndrome but lack of accuracy to predict AD pathology.

**Keywords.** Alzheimer's disease, AD pathology, FCSRT, Free & Cued, Memory, Amnesia

**Introduction**

Amnesia is a central feature of Alzheimer's disease (AD) and belongs to the earliest and most prominent symptoms of typical AD. In the last decades, characterisation of the memory impairment due to AD came as a major diagnosis advance, when pathophysiological biomarkers were still in their infancy (Grober & Buschke, 1987; Pasquier et al., 2001; Dubois et al., 2004). Free and cued memory tests, in particular, allowed the delineation of different components of memory (Grober & Buschke, 1987). Amnesia, when characterized by storage difficulties, was shown to be the best clinical marker of typical AD (Pasquier et al., 2001; Sarazin et al., 2007; Teichmann et al., 2017). This assumed specificity of amnesia to AD strongly impacted the field and helped to identify typical AD in health care settings. While nowadays, most expert centres would rather base AD diagnosis on biomarkers (Jack et al., 2018), amnesia remains an important dimension in primary care settings, as investigations aiming to detect amyloid and tau pathologies are expensive and invasive.

However, the excessive confidence in the specificity of amnesia may also have negatively impacted the differential dementia diagnosis (Hornberger & Piguet, 2012), as the presence of severe amnesia in frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), vascular dementia (VaD)(Elfrgen et al., 1993; Kraybill et al., 2005; Graham et al., 2005; Jicha et al., 2006; Reed et al., 2007; Mathias & Burke, 2009; Hornberger et al., 2010; Hornberger et al., 2012; Yoshizawa et al., 2013; Bertoux et al., 2014; Petrova et al., 2015; Salmon et al., 2015) and psychiatric cases has been since reported (Kizilbash et al., 2002; Lee et al., 2012). Moreover, most of the studies assessing amnesia in AD lacked pathological confirmation (Pasquier et al., 2001; Sarazin et al., 2007; Teichmann et al., 2017). This issue is not trivial as describing the memory profile of clinically-defined AD raises a circular

reasoning bias, contributing to overestimate the diagnostic accuracy of amnesia (Castilhos & Chaves, 2017).

In this context, both hypothesis-free data-driven methods and clinicopathological correlation studies may provide new knowledge on both the clinical relevance of amnesia and the diagnostic value of memory tests such as the Free and Cued Selective Reminding Test (FCSRT) to predict AD pathology. The aim of this study was to use data-driven clustering on neuropathological data to test in an unbiased way the diagnostic value and accuracy of amnesia to predict AD among other neurodegenerative conditions.

## Material and methods

*1.1 Selection of participants (inclusion criteria)*

Patients were seen at referral (at first presentation) in a tertiary care memory clinic setting in Bordeaux, Lille, Marseille, Paris and Rouen. They had an initial Mini Mental State Examination (MMSE – Folstein et al., 1975) score ≥20/30 during this first visit and a memory assessment with the FCSRT within six months of this initial visit. All were followed-up until death and received a diagnosis of dementia prior to death. They volunteered for brain donation (information was given regardless of the clinical presentation) and signed informed consents. On this basis, 91 patients were included. Patients had been followed-up at Lille (87,4%), Paris (9.5%), Rouen (1.9%), Marseille (0.7%) and Bordeaux (0.4%) University Hospitals. Autopsies were performed between 1993 and 2017. Patients records were stored at the Lille brain bank (Lille Neurobank, Lille) and the Neuro-CEB brain bank.

*1.2 Standards Protocol Approvals, Registrations and Patient Consents*

The institutional review board of the Lille Neurobank of Lille University Hospital approved the study. All patients or their relatives signed written informed consent to participate in the study.

*1.3 Histopathologic procedures*

All cases underwent autopsy and neuropathologic examination by neuropathologists. Postmortem delay ranged from 4 to 30 hours. Most of the right hemisphere was frozen for subsequent biochemical and molecular biology analysis. The whole left hemisphere, brainstem, cerebellum, and samples from the right hemisphere were fixed in 10% buffered formalin for histopathology and immunohistochemistry (tau protein, beta-amyloid,

alphasynuclein, TDP-43, and prion protein). Tissue samples were taken from multiple cortical areas (Brodmann areas 4, 8/9, 10, 20/21, 38, 39, 40, 17, 18, 23, and 24), hippocampus, amygdala, nucleus basalis, basal ganglia, brainstem, cervical spinal cord, and cerebellum. Cerebrovascular scoring (including the semi quantification of arteriolosclerosis, amyloid angiopathy, perivascular space widening, myelin loss in the white matter, microinfarcts, and large infarcts) was made on 3 large coronal slides from the frontal lobe, the temporal lobe and basal ganglia region, after hematoxylin-eosin and Luxol fast blue staining (see Deramecourt et al., 2014). The clinical contribution of cerebrovascular lesions was considered as probable (vascular dementia or mixed dementia) in cases with a cerebrovascular score strictly above 10/20. Vascular lesions were evaluated as described before (Deramecourt et al., 2014); in our study, cases characterized by significant arterosclerosis will be noted VaD and amyloid angiopathy will be noted AA. Mixed pathology was systematically reported and involved the co-occurrence of two or more different pathologies. The respective pathological diagnostic criteria were used depending on the disease: AD (Hyman et al., 2012), DLB (McKeith et al., 2017), FTLD (Mackenzie et al., 2009) and Creuzfeldt-Jakob disease (CJD) (Budka et al., 1995).

*1.4 Clinical assessment*

The initial symptoms reported by patients or carers at presentation were encoded from the clinical records.

All participants underwent the French version of the FCSRT (Van der linden et al., 2004), which evaluates the ability to learn and recall a list of 16 written words. A first phase involves the learning of the words. During this phase, 4 x 4 groups of words were presented. Semantic cues were then given and participants had to associate the given cue (e.g. profession) to one of the 4 word presented (e.g. dentist) sequentially. Then, words were hidden and the semantic

cues were used to control for memory encoding or immediate recall of the 4 words (e.g. "What was the profession?"). Memory recall is then evaluated by asking to retrieve the words, first spontaneously (free recall), then with the help of the semantic cues of a supraordinal taxonomic category for items that were not retrieved (cued recall). This phase is repeated twice. During these phases, if participants failed to retrieve the item with the category cue, they were reminded by presenting the cue and the item together. Total free recall and a total (free+cued) recall scores as well as an index of sensitivity to semantic cues ((total free recall score – total recall score)/(total recall score - 48)) are computed from this phase. Following a delay of 20-30 min, a final recall trial is performed, providing free, cued and total delayed recall scores.

General cognitive functioning was assessed with the Mattis Dementia Rating Scale (MDRS – Mattis, 1988), an objective general cognitive battery widely used for the assessment of neurodegenerative conditions and staging of cognitive decline. The MDRS examines five cognitive domains (attention, initiation, construction, conceptualization, memory).

*1.5 Statistical analyses*

Statistical analyses were conducted with SPSS 20 (IBM, 2015). Univariate non-parametric (Kruskal-Wallis) ANOVA was used to assess group differences followed by Mann-Whitney test for two-by-two comparisons (or Chi-Squared test in case of binomial variables) because of non-normal data. Bonferroni corrections were applied to all statistical comparisons to correct for multiple comparisons. In order to determine the cluster architecture of memory performance in patients, a hierarchical clustering analysis using Ward's method was first employed on the standardized FCSRT's total scores (i.e. total free recall, total recall, sensitivity to cues and total delayed recall scores), based on Squared Euclidian Distance with a dendrogram examination. A Two-step clustering analysis based on a Bayesian Information

Criteria was then used to match the different patients' clusters of memory performance to the histological diagnoses. In the first step, the Bayesian Information Criteria for each number of clusters within a specified range was performed and considered to find an initial estimate for the number of clusters. The second step refined the initial estimate by finding the greatest change in distance between the two closest clusters in each hierarchical clustering stage. Reports of the cluster analyses followed consensual recommendations (Clatworthy et al., 2005). As an analysis of the prediction value of the presence of absence of AD pathology, we employed binary logistic regression (Enter method). Akaike Information Criterion (AIC) was computed as an estimator of models' quality (lower AIC means higher quality) when the model prediction was significant. Receiver operating characteristic (ROC) curves were employed to identify patients with AD pathology based on each FCSRT score.

## Results

### *2.1 Study population*

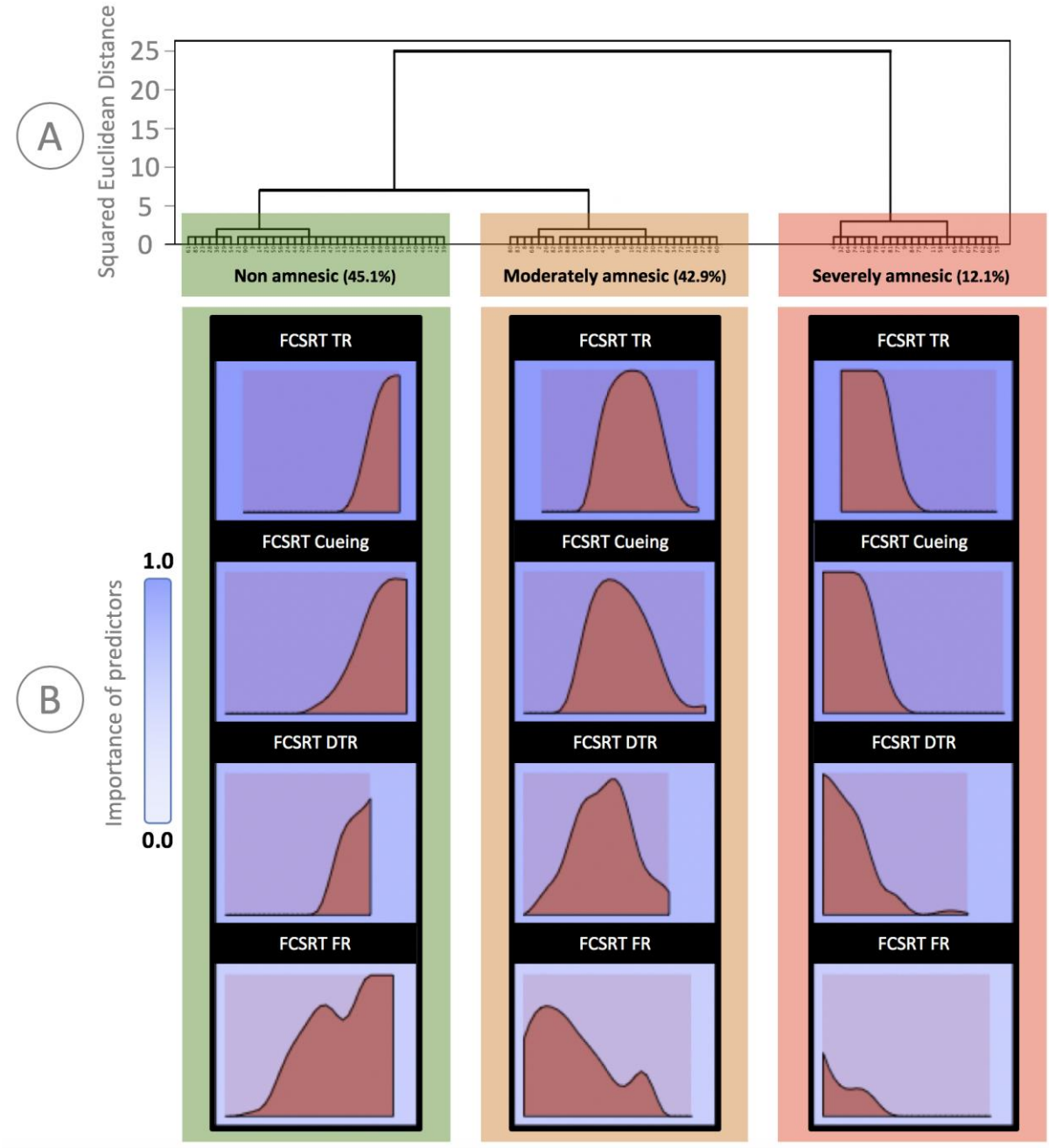
On the whole population, the mean age at disease onset (age at first symptoms) was 65.07 ± 9.84 years. The delay between symptoms onset and the first referral was 2.28 ± 2.07 years and the mean disease duration (from symptoms onset to death) was 9.05 ± 4.46 years. Three levels of education were categorised: primary (45.7% of patients), high school (22.2%) and graduate education (32.1%). Initial MMSE score at presentation was 25.53 ± 2.81.

Final neuropathologic diagnoses consisted of 15 (16.5%) pure AD, 26 (28.6%) mixed AD and 50 (54.9%) non-AD cases. Pure AD and mixed AD cases were all characterized by severe levels of neurofibrillary pathology (Braak stages ≥5). Mixed AD (mAD) cases included AD+VAD (n=9), AD+LBD (n=9), AD+FTLD (n=2), AD+AA (n=2) and AD+≥2 associated pathologies (n=4). Non-AD cases were FTLD (n=36), VaD (n=9), CJD (n=2) or mixed pathology such as LBD & VaD (n=3) cases. Six patients (6.6%) had FTLD caused by a

mutation in *GRN* (n=2) or *C9orf72* (n=4) genes. Mixed-AD patients were older than Pure-AD and Non-AD patients (Z=-3.218; p=.001). Memory impairment reported at onset was more frequent in Mixed-AD in comparison to Non-AD ($\chi^2$=8.483; p=.004). Other variables were not statistically different across the three groups (all $\chi^2$<6.5; p>.02) (Table 1).

A single symptom was reported in 49.45% of cases, two symptoms were reported in 38.46% of cases and ≥3 symptoms were reported in 6.59% of cases. In 5.49% of cases, first symptoms were missing from the records. At first visit, memory impairment was reported in 60.41% of patients, followed by behaviour and psychological symptoms (e.g. anxiety, sadness, hallucinations) in 27.47%, language impairments (24.17%), and motor symptoms (7.69%). These symptoms were all based on carers reports.

*#Please insert Table 1 around here*




*2.2 Memory performance clustering (Figure 1.A; Table 2)*

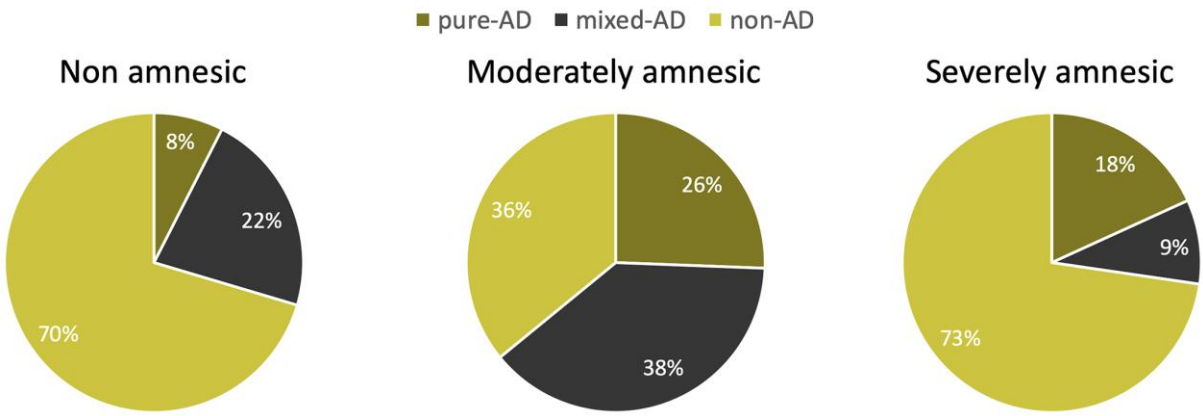
The hierarchical clustering analysis revealed the existence of three clusters of patients: (1) non-amnesic (45.1% of patients), (2) moderately amnesic (42.9%) and (3) severely amnesic (12.1%). This cluster architecture was validated independently with the memory score of the MDRS. There were significant differences between clusters ($F=12.470$; $p<.00005$) on this memory score with the following pattern: non-amnesic > moderately amnesic > severely amnesic. Importantly, when considering normative data of the FCSRT total recall score, none

of the patients in the non-amnesic cluster could be considered as being amnesic. There were no differences between MMSE score ($\chi^2$=3.261; p=.19), age ($\chi^2$=0.841; p=.66), time to referral ($\chi^2$=1.663; p=.43) and gender ($\chi^2$=4.531; p=.10) between clusters. A non-significant statistical trend was observed on education ($\chi^2$=10.431; $p=.005_{uncorrected}$), with patients in the non-amnesic cluster having better education levels than those in the moderately (Z=-2.733; $p=.006_{uncorrected}$) and severely amnesic clusters (Z=-2.378; $p=.025_{uncorrected}$), the latter ones showing no differences between each other (Z=-.799; p=.51). No interactions between the different variables were found.

*#Please insert Table 2 around here*

*2.3 Matching between memory performance clusters and pathological diagnoses*

The two-step cluster analysis presented a good cluster quality (Silhouette coefficient >.05). As shown on Figure 1.B, FCSRT total recall has the best (=1,00) inter-class predictor importance (indicating how well the variable can differentiate different clusters) followed by sensitivity to cues (.86), delayed total recall (.61) and free recall (.36). The "non-amnesic" cluster was composed of 41 patients including three (7.3%) pure-AD, 10 (24.4%) mixed-AD and 28 (68.3%) non-AD patients. The "moderately amnesic" cluster was composed of 39 patients including 10 (25.6%) pure-AD, 15 (38.5%) mixed-AD and 14 (35.9%) non-AD patients. The "severely amnesic" cluster was composed of 11 patients including two (18.2%) pure-AD, one (9.1%) mixed-AD and eight (72.7%) non-AD patients. The distribution of diagnoses in the three clusters is presented on figure 2, table 2 and shows significant differences in the proportions of patients in each cluster for Pure-AD and Mixed-AD compared to Non-AD ($\chi^2$=11.678; p<.05).




In order to provide a more detailed matching between the clusters and the pathological diagnoses, we divided the non-AD pathological diagnoses into FTLD, VaD and other pathologies (this last group including CJD and LBD mixed with VaD) and crossed refined pathological diagnoses with the obtained memory clusters. A significant proportion of patients with non-AD pathology was either moderately or severely amnesic at presentation (44.4% of FTLD, 55.6% of VaD and 20% of other pathologies patients) (table 3).

*#Please insert Table 3 around here*

*2.4 Data-driven prediction of AD pathology*

We then used the FCSRT scores considered in the cluster analyses as a set of predictors for the presence of AD pathology in a binary logistic regression. The best data-driven prediction reached an accuracy of 70.3% ($\chi^2$=12.46; AIC=118.79; p<.05), meaning that the presence of AD pathology could only be correctly predicted in 70.3% of cases on the basis of the FCSRT four main scores. This model reached a sensitivity of 65.2% and a specificity of 75.6%, with a positive predictive value of 73.2 % and 17.6% of cases being identified as false positive cases (16/91 patients). In order to evaluate the capacity of each FCRST score to discriminate cases with AD pathology from those without AD pathology, optimal receiver operating

characteristic curves were computed. Optimum areas under the curve (AUC) were defined using the highest Youden index (optimizing both sensitivity and specificity of diagnosis). AUC for free recall (.390), total recall (.377), sensitivity to cues (.391) and delayed total recall (.400) were low. Only total recall (p=.028) and sensitivity to cues (p=.045) were significant discriminants.

We then sought to determine whether the FCSRT prediction of AD pathology was similar when analyses were restricted to patients for which memory impairment was the main complaint at presentation. The prediction accuracy reached 66.7% ($\chi^2$=8.314; p=.08), increasing the initial sensitivity to 83.9% and decreasing the specificity to 43.5% (24.1% of false positive cases in this sample, or 13/54 patients) in comparison with the data-driven prediction of AD pathology (-3.7% of accuracy, +18,7% of sensitivity, -32.1% of specificity).

**Discussion**

The aim of this study was to assess the predictive value of amnesia for AD among 91 patients examined in the early stages of cognitive decline and followed until autopsy. We based our investigations on the FCSRT, a reference tool to explore the different components of verbal memory (Grober & Buschke, 1987; Van der Linden et al., 2004). Using an unbiased data-driven approach, we studied the correspondence between FCSRT memory profiles and the pathological diagnoses. The predictive value of the FCSRT for AD was assessed as well. In this study, the use of the FCSRT, relying on semantic cues during learning and recall, allowed to identify “pure” amnesia among the patients, i.e. a typical impairment of memory storage and not only difficulties in retrieval processes. Data-driven clustering revealed three distinct clusters of performance reflecting different levels of amnesia. However, there was little correspondence between these clusters and AD pathology, since a third of patients with pure

and mixed AD pathology were non-amnesic at presentation and nearly half of patients devoid of AD pathology were amnesic. In addition, data-driven prediction of AD pathology based on FCSRT scores had only a low accuracy (70.3%).

Overall, the findings of this study suggest that despite its usefulness to identify amnesia, the FCSRT is of limited value to specifically diagnose AD pathology. Our results show that this symptom is too frequently observed in other diseases to accurately support the clinical diagnosis of AD. While discussing the neural mechanisms at stake in amnesia is outside the scope of our study, we think that the implicit association between amnesia, AD and hippocampus degeneration led to the common belief that amnesia is a specific symptom of AD, which is still vividly present in clinical practice and scientific literature (Sarazin et al., 2007; Teichmann et al., 2017; Jahn, 2013; Maruszak & Thuret, 2014). Indeed, progressive pathological changes due to AD are now well characterized. Since the early 1990s, the hippocampus complex is known to be affected early during the course of the disease (Braak & Braak, 1997; Craig et al., 2011). Years before, identification and characterization of memory deficits after bilateral surgical lesions of the mesial temporal lobe demonstrated the importance of the hippocampus in memory processing (Squire, 2004). The hippocampal complex was then established as the core anatomical component of the declarative memory system (Squire, 2004). As highlighted by others (Aggleton et al., 2016), the historical assumption that the medial temporal lobe is the key structure for episodic memory has contributed to link memory loss in AD to the hippocampus complex, leading some to consider AD as a hippocampal dementia (Craig et al., 2011). In this context, tests assessing episodic-like memory, thought to assess the function of the hippocampus complex, have been increasingly used as an early marker of AD and amnesia was eventually considered as the core clinical feature of typical AD. This overlap between amnesia, AD and hippocampal

dysfunctions led some authors to hypothesize the existence of an "amnestic syndrome of hippocampal type" (Dubois et al., 2004; Sarazin et al., 2007; Xie et al., 2014) or in other words, a cognitive syndrome characterized by memory storage difficulties due to hippocampal atrophy, that would be specific to AD. Cued memory paradigms and the FCSRT in particular, were then subsequently used to track the conversion from MCI to AD (Sarazin et al., 2007), as well as for the positive (Dubois et al., 2004, 2014; Xie et al., 2014) and differential diagnosis of AD (Pasquier et al., 2001; Teichmann et al., 2017; Lemos et al., 2014).

Our findings set limitations to this approach. Using a data-driven clustering method, we were able to divide our population into three groups with absent, moderate and severe amnesia according to the FCSRT memory scores obtained at an early stage of cognitive decline. However, there was a limited correspondence with AD pathology. In the severely amnesic cluster, non-AD patients were three times as much as AD patients. Nearly half of patients with FTLD and VaD patients were classified in the amnesic clusters. There is however an ambiguity regarding whether amnesia should be considered as a marker of AD pathology (Dubois et al., 2014) or typical AD (Sarazin et al., 2007), *i.e.* AD with an amnesic presentation. To take the latter into account, we then restricted the analysis to patients with memory complaint at presentation. Both approaches showed a similarly poor accuracy of FCSRT to predict AD, showing that our results were not biased by an over-representation of atypical AD cases. These findings are in line with previous reports made on cohorts with a pathological confirmation of diagnoses. Indeed, numerous studies suggested that severe amnesia could be observed in patients with non-AD or mixed AD pathology, such as DLB (Kraybill et al., 2005; Yoshizawa et al., 2013; Salmon et al., 2015), FTLD (Elgren et al., 1993; Grahan et al., 2005; Hornberger et al., 2012), or to a lesser degree VaD (Jicha et al.,

2006; Reed et al., 2007). This last decade, memory impairment was reported in clinically-defined DLB (Petrova et al., 2015; Molano et al., 2010), in the clinical subtypes of FTLD such as behavioural variant frontotemporal dementia (Hornberger et al., 2010; Bertoux et al., 2014), semantic progressive aphasia (Casaletto et al., 2017), non-fluent progressive aphasia (Ramanan et al., 2016), amyotrophic lateral sclerosis (Mantovan et al., 2003), progressive supranuclear palsy (Kobylecki et al., 2015) as well as in clinically-defined VaD (Mathias & Burke, 2009) although inconsistent findings were reported in this disease due to the variable topography of vascular lesions. Not least of all, severe amnesia is also the main feature of hippocampal sclerosis, often related to aberrant TDP-43 immunohistochemistry (Nelson et al., 2019). Limbic-predominant age-related TDP-43 encephalopathy (LATE) with or without hippocampal sclerosis affects 20% to 50% of individuals past age 80 years, according to large community-based autopsy series (reviewed in Nelson et al., 2019). The recent recognition of LATE as one of the common age-related diseases that can mimic the amnestic presentation of AD hence came as a major breakthrough (Nelson et al., 2013), demonstrating that AD is not the sole cause of amnesia, even in the 'oldest old'.

Taken together, these reports and our findings plead against the exclusivity of amnesia to AD. Amnesia should be conceived as a common symptom of neurodegenerative disease, rather than a reliable indication of AD pathology.

This study is the first to specifically investigate the accuracy of amnesia to predict AD pathology in a cohort with various pathologically confirmed aetiologies. While we believe that the reasonable sample size, the inclusion of patients at early or mild dementia stages, the use of the FCSRT at presentation as well as the utilization of data-driven procedures are strengths to this study, we also acknowledge some limitations. In particular, our cohort may not be representative of all patients with progressive neurocognitive disorders. The patients

included in this study were seen in tertiary centres and therefore, may be more atypical. Indeed, the proportion of pure-AD patients is smaller than the proportion of non-AD patients, the age of onset is younger than usual cohorts and the gender ratio is atypical in the AD group. This particular recruitment might have led to an underrepresentation of typical amnesic AD and an overrepresentation of atypical patients, such as non-amnesic AD and amnesic non-AD patients. Although the majority of patients were recruited from a centre where information on the possibility of brain donation is given very widely, regardless of the atypical presentation, one cannot exclude that patients and families are more willing to brain autopsy when the clinical diagnosis has been debated. However, the ancillary analysis on the subset of patients that had memory complaints at first referral (simulating the commonest context in which the presence of AD pathology is suspected) showed similar prediction accuracy with the analysis conducted in the whole population.

Because a single test was employed to assess the presence of amnesia in this study, one could question the generalization of our findings and argue that different tests could have led to different results. This is a relevant question given that previous studies have shown the marginal ability of the FCSRT to distinguish clinical AD from behavioural variant of FTLD in particular (Bertoux et al., 2014). Indeed, FTLD cases represented 72% of non-AD cases in this study, and among them, 64% received a clinical diagnosis of a behavioural variant FTLD and 14% a clinical diagnosis of AD. Among AD cases, 13% received a clinical diagnosis of behavioural variant FTLD. First, we believe that considering a single rather than several verbal memory tests is an approach that is closer to the clinical practice, where time is limited and other cognitive domains have to be assessed, although the best practice would have been to combine our exploration with another (e.g. spatial) qualitatively different measure of memory. The FCSRT is commonly used by neuropsychologists as it involved both free and

cued-based recalls, thus allowing us to tackle the commonest criticize made to studies only addressing free recall. In addition, the poor discrimination power of memory testing in the context of the differential diagnosis between AD and FTLD, although it was never the focus of a neuropathological study before, has been shown independently of the test used and the memory component explored (Bertoux et al. 2018; Poos et al., 2018). In consequence, we believe that it is likely that our findings could be generalizable with other common verbal memory assessment. However, given that the prediction accuracy was only based on a single memory test, we cannot rule out that only the sensitivity and specificity to AD of verbal amnesia, and not amnesia in general, have been explored in our study.

The approach to consider a single measure raises another point of discussion: whether or not, in specialized memory clinics, memory assessment is considered alone to inform diagnostic decisions. To this question, the definitive answer is no, as neuropsychologists and specialized neurologists would rather consider a general behavioural and neuropsychological profile relying on multiple cognitive domains. We thus acknowledge that our approach, relying on a single measure to predict the underlying pathology, does not realistically fit the clinical practices occurring in specialized centres – although it was not the aim of this study to do so.

As mentioned above, the implicit association between amnesia, AD and hippocampus degeneration led to the common belief that amnesia is a specific symptom of AD. In that perspective, medical tests based on shortened version of the FCSRT have been used increasingly by physicians outside specialized centres in the last years to screen for AD specifically (Cowppli-Bony et al. 2005). Our findings, showing that verbal amnesia is a common symptom of neurodegenerative diseases and therefore does not predict AD pathology specifically, contradict what likely became over the year a clinical heuristic commonly used by clinicians. What is at stake here is not a shift in expert centres' practices, but rather higher caution warranted outside specialized centres, where the diagnosis relies on

less exams and expertise. To follow the best neuropsychological practices, future studies that would aim to replicate our findings should consider the FCSRT – or any other verbal episodic-like memory test – together with another qualitatively different memory measure (such as visual or spatial memory).

This study has important implications for the early diagnosis. Early diagnosis offers the opportunity for timely interventions, coordinated care plans and better management of symptoms. Experts agree to consider early diagnosis a cost-saving approach, through a reduction in preventable hospitalization, simplification of the medication regimen and postponement of institutionalization (Alzheimer's Association, 2018). However, a correct diagnosis is paramount to allocate healthcare resources in an equitable and cost-effective fashion. In that regard, clinical diagnosis of AD is not sufficiently accurate: up to 50% of patients with mild cognitive impairment and 25% of those with mild dementia recruited in AD clinical trials do not meet biomarker criteria for AD (Sevigny et al., 2016). Differential AD diagnosis is highly relevant since pharmacotherapy and prognosis differ in AD mimics. Our findings thus support the use of CSF and imaging biomarkers (Jack et al., 2018). However, a thorough diagnostic workup is still a costly venture. It can reach up to $5000 in the early stages, assuming all available diagnostic procedures are done (Winblad et al., 2016), a difficult cost to sustain for most healthcare systems, even when counterbalancing the putative long-term economies. Improving the accuracy of early clinical diagnosis is therefore an outstanding issue. We herein demonstrate that AD clinical diagnosis cannot rely solely on the memory profile or severity of amnesia. This highlights the importance to examine behaviour and other cognitive domains in addition to memory during a diagnosis-oriented neuropsychological assessment or screening (Albert et al., 2011). What is also highlighted here is the common limitations of current memory assessment in the field of

neurodegeneration. Limited ecological validity of word-list based tests and their lack of an episodic character should be considered as well as other novel or unexplored cognitive processes to take up the biggest challenge of modern neuropsychology within our field: providing a set of measures able to accurately predict the underlying pathology. This "molecular neuropsychology" should go way beyond classical tasks and classical assumption of specific impairments. By summing up the past findings and bringing a pathological confirmation of the non-specificity of memory impairment to AD, we believe that the current study participated in this fresh start.

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| | **Pure-AD** | **Mixed-AD** | **Non-AD** |
|---|---|---|---|
| Age | 69.7 (10.9) | 71.9 (7.3) * | 65.1 (9.9) |
| Gender (W/M) | 46.7% / 53.3% | 53.8% / 46.2% * | 24% / 76% |
| Level of education | | | |
| *Primary* | 33.3% | 52.0% | 44.9% |
| *Secondary* | 26.7% | 20.0% | 28.6% |
| *Graduate* | 40.0% | 28.0% | 26.5% |
| Time (years) to referral | 2.6 (2.5) | 2.1 (2.5) | 2.5 (2.2) |
| Total (years) disease duration | 11.07 (5.3) | 8.2 (4.1) | 8.8 (4.3) |
| MMSE | 25.7 (2.2) | 24.7 (2.9) | 25.9 (2.9) |
| Initial symptoms reported by carers | | | |
| *Memory impairment* | 66.6% | 73.1% * | 54.0% |
| *Behavioral and psychological symptoms* | 26.7% | 19.2% | 30.0% |
| *Language impairment* | 26.7% | 11.5% | 30.0% |
| *Motor symptoms* | 0.0% | 7.7% | 10.0% |

Table 1 – Demographics, Mini Mental State Examination (MMSE) score and initial symptoms reported by careers at presentation. * Significant difference with Non-AD

| Clusters | Total Free | Total Recall | Cueing (%) | Delayed Total |
|---|---|---|---|---|

| | Recall (/48) | (/48) | | Recall (/16) |
|---|---|---|---|---|
| Non-Amnesic | 20.27 ± 6.14 | 44.85 ± 2.81 | 88.61 ± 10.47 | 15.27 ± 1.00 |
| Moderately Amnesic | 11.28 ± 4.55 | 32.54 ± 5.40 | 57.77 ± 13.10 | 10.46 ± 3.05 |
| Severe Amnesic | 5.09 ± 4.55 | 12.91 ± 5.54 | 18.04 ± 10.93 | 4 ± 4.34 |

Table 2 – Average score (and standard deviation) for each cluster defined group on the four FCSRT measures considered in the cluster analyses.

| | **Pure-AD** | **Mixed-AD** | **Non-AD** |
|---|---|---|---|
| Non-amnesic | 20.0% * (3) | 38.5% (10) | 56.0% (28) |
| Moderately amnesic | 66.7% * (10) | 57.7% * (15) | 28% (14) |
| Severely amnesic | 13.3% (2) | 3.8% (1) | 16% (8) |
| | | | |
| Amnesic (moderately + severely) | 80% * (12) | 61.5% (16) | 44% (22) |

Table 3 – Proportion (number) of non-amnesic, moderately amnesic, severely amnesic and amnesic (i.e. moderately+severely) patients within the different pathological groups as identified by the clustering analysis. * Significant difference with Non-AD.

## Figures title & legends

Figure 1 – (A) Dendrogram using Ward's linkage based on squared Euclidean distance showing the cluster architecture of the 91 patients divided into three distinct clusters composed from non-amnesic (45.1%), moderately amnesic (42.9%) and severely amnesic (12.1%) patients. (B) Relative distribution of neuropsychological scores employed as inter-clusters predictors and classified according to their level of importance. Frequency is on the vertical axis and FCSRT score on the horizontal (with lowest score on the left). FCSRT=Free & Cued Selective Remining Test; TR=Total Recall; Cueing=Sensitivity to cues; DTR=Delayed Total Recall; FR=Free Recall.

Figure 2 – Distribution of pure-AD, mixed-AD and non-AD neuropathological diagnoses in the three clusters of memory performance according to the FCSRT.

Figures should be printed in black and white.