Two Distinct Amnesic Profiles in Behavioral Variant Frontotemporal Dementia

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Background: Whether or not episodic memory deficit is a characteristic of behavioral variant frontotemporal dementia (bvFTD) is a crucial question for its diagnosis and management.

Methods: We compared the episodic memory performance profile of bvFTD patients with healthy control subjects and patients with Alzheimer's disease (AD) as defined by clinical and biological criteria. Episodic memory was assessed with the Free and Cued Selective Reminding Test, which controls for effective encoding and identifies memory storage ability resulting from consolidation processing. One hundred thirty-four participants were evaluated: 56 patients with typical clinical presentation of AD and pathophysiological evidence as defined by cerebrospinal fluid AD biomarker profile and/or significant amyloid retention on Pittsburgh Compound B positron emission tomography; 56 patients diagnosed with bvFTD with no evidence of AD-cerebrospinal fluid biomarkers when a profile was available (28/56), including 44 progressive (bvFTD) and 12 nonprogressive (phenocopies) patients; and 22 control subjects with negative amyloid imaging.

Results: Memory scores could not differentiate bvFTD from AD patients (sensitivity and specificity $<50\%$). Taking into account the individual distribution of Free and Cued Selective Reminding Test scores, half of bvFTD patients had a deficit of free recall, total (free + cued) recall, and delayed recall as severe as AD patients. The other half had subnormal scores similar to phenocopies and a delayed recall score similar to control subjects.

Conclusions: We observed two distinct amnesic profiles in bvFTD patients that could reflect two types of hippocampal structure and Papez circuit involvement. These findings on episodic memory profiles could contribute to discussions on the recent international consensus criteria for bvFTD.

Key Words: Alzheimer's disease, amnesia, diagnosis, episodic memory, frontotemporal dementia, neuropsychology

The revised criteria for the diagnosis of behavioral variant frontotemporal dementia (bvFTD) are based on behavioral features and a neuropsychological profile that include a relative sparing of episodic memory (1). Severe amnesia is thus considered as an exclusion criterion to meet the neuropsychological criterion for bvFTD, but studies with postmortem neuropathological diagnosis confirmation have shown that bvFTD patients may manifest severe episodic memory deficits, even at initial presentation (2–4). More recently, several studies have demonstrated that episodic memory deficits are more common in bvFTD than previously believed and that they may even be as severe as in Alzheimer's disease (AD) (5,6). Because the severe amnesia observed in bvFTD contrasts with the preserved memory performance of phenocopy patients, who display typical behavioral features of bvFTD but do not progress to dementia (7), it has been suggested that the admixture of phenocopy and bvFTD could have led to an underestimation of memory impairment in previous studies of bvFTD (8,9).

Moreover, imaging studies have shown that hippocampal structures and the Papez circuit are affected in bvFTD, suggesting that amnesia could be due to defects in memory storage and consolidation processing (9–11) rather than a deficit of frontal lobe-based strategies of memory recall, as was previously suggested (12,13). One way to assess which of these subprocesses of episodic memory is compromised in bvFTD is to explore memory performance with the Free and Cued Selective Reminding Test (FCSRT), a test that can control for effective encoding and identify memory storage associated with consolidation processing. This test provides objective measures of the main subprocesses of episodic memory: 1) encoding, i.e., immediate registration of the item, which involves attentional processes; 2) consolidation, i.e., formation of a memory trace; and 3) the retrieval of the learned material. The cued recall technique used in the FCSRT aims at enhancing both the encoding and the retrieval phases, to minimize the effect of impaired attention and inefficient retrieval strategies due to executive dysfunction and therefore to identify a pure memory deficit.

In this context, we aimed to analyze episodic memory function in a large group of bvFTD patients comparatively with AD patients selected according to clinical and biological criteria to ensure exclusion of patients with atypical AD or atypical bvFTD with AD etiology.

Methods and Materials

Participants

One hundred thirty-four participants were selected from the database of the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital from May 2007 to June 2012, including

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Received May 17, 2013; revised Jul 29, 2013; accepted Aug 15, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.08.017

the Biomage (ANR-07-LVIE-002-01) and Imabio3 studies (Programme Hospitalier de Recherche Clinique 2010). Fifty-six AD patients were selected according to the following criteria: 1) typical clinical presentation of AD with an amnestic presentation; and 2) biological evidence of the AD pathophysiological process as defined by cerebrospinal fluid (CSF)-AD biomarker profile and/or significant amyloid retention on positron emission tomography (PET) with ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB). A CSF-AD biomarker profile was defined as a phosphorylated tau/amyloid beta 42 ($A\beta_{42}$) ratio greater than .21, which distinguishes AD from bvFTD with high sensitivity (91.2%) and specificity (92.6%) (14). Significant fixation of ^{11}C-PiB on PET was defined by a global index higher than 1.4. All patients underwent lumbar puncture (LP); 18 patients underwent both LP and ^{11}C-PiB-PET.

Fifty-six bvFTD patients met the following inclusion criteria: prominent changes in personality and social behavior according to the core clinical diagnostic criteria for frontotemporal dementia (FTD) (1) and normal CSF biomarker profile as defined by a phosphorylated tau/$A\beta_{42}$ ratio lower than .21 when LP was performed (n = 28/56). We included patients with memory impairment if the other core diagnostic criteria of bvFTD were present. None of the patients had a family history of dementia. As we aimed to distinguish bvFTD from phenocopies, we classed patients diagnosed with bvFTD according to their clinical progression during at least 3 years of follow-up. Among the 56 patients, 44 showed clinical progression consistent with the diagnosis of bvFTD based on cognitive measures (Mini Mental State Examination [MMSE] and Mattis Dementia Rating Scale [MDRS]) (15,16) and activities of daily living during at least 3 years of follow-up; these 44 patients constitute the bvFTD group. The 12 remaining patients showed no change in cognitive measures and activities of daily living over a 3-year period and were therefore classified as phenocopies.

Twenty-two normal control subjects were selected according to the following criteria: 1) MMSE ≥27 and normal neuropsychological testing; 2) negative amyloid imaging on ^{11}C-PiB-PET, as defined by a global ^{11}C-PiB retention index lower than 1.4; and 3) no history of psychiatric or neurologic conditions.

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, 3) severe depression, or 4) motor neuron disease.

Measurement of CSF Biomarkers

Cerebrospinal fluid samples were collected by LP and analyzed for total tau, tau phosphorylated at threonine 181, and $A\beta_{42}$ using a double-sandwich enzyme-linked immunosorbent assay method (Innogenetics, Gent, Belgium). Assays were conducted at the Metabolic Biochemistry Department of the Pitié-Salpêtrière Hospital, as described elsewhere (14).

^{11}C-PiB PET Imaging Procedures

Positron emission tomography imaging with ^{11}C-PiB was performed in all control subjects and in 21 AD patients. The method was the same as previously described (17). In summary, a global cortical index was defined by the mean standard uptake value ratio (with the cerebellum as the reference region) of the following cortical regions: 1) frontal cortex, by grouping the orbitofrontal, polar prefrontal, and dorsolateral cortex; 2) anterior cingulate; 3) medial cingulate; 4) posterior cingulate; 5) precuneus; 6) occipital cortex, by grouping the calcarine cortex, occipital cortex, and cuneus; 7) temporal cortex, by grouping the anterior and lateral temporal cortex; 8) hippocampus; and 9) parietal cortex, by grouping the inferior and superior parietal cortex and the parietotemporal junction.

Neuropsychological Assessment

All subjects underwent a neuropsychological assessment that included the MMSE, the Frontal Assessment Battery (FAB) (18), semantic/morphologic verbal fluencies, and the FCSRT (see below) (19). In addition, patients in the bvFTD and phenocopy groups were tested with a frontal battery including the MDRS, the modified Wisconsin Card Sorting Task (20), the digit span forward and backward for verbal working memory, the short version of the Social cognition and Emotional Assessment (21) for social cognition, and a picture denomination task to identify semantic memory deficits.

Assessment of Episodic Memory in All Participants. The FCSRT (19) was selected because it is based on a semantic cueing method that controls for effective encoding of the list of words and facilitates retrieval by semantic cueing. The FCSRT was administered according to the procedure previously described by Sarazin *et al.* (22). Immediate cued recall was tested in a first phase to control for encoding (16 written words presented in groups of 4 × 4, maximum score = 16). Then, the memory phase was performed in three successive recall trials. Each recall 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 patient. The same semantic cue given in the initial encoding stage was used. This provided a free recall score and a total (free + cued) recall score (maximum score = 48). Then, after an interval of 30 minutes, a last recall trial was performed, providing free and total delayed recall scores (maximum score = 16).

All control subjects and AD patients were included in either the Biomage or Imabio3 studies, which were both approved by the Ethics Committee of the Pitié-Salpêtrière Hospital, and participants provided written informed consent before participating. For all other patients, the biological, clinical, and imaging data were generated during routine clinical workups 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.

Statistical Analysis

Data were analyzed using SPSS20 (SPSS Inc., Chicago, Illinois). Before any analysis, variables were plotted and checked for normality of distribution using the Shapiro-Wilk test. Parametric data were compared across the four groups via analysis of variance, followed by Student t test. Nonparametric data were analyzed by Kruskal-Wallis analysis of variance followed by the Mann-Whitney test for two-by-two comparisons. We used Spearman's rank coefficient for correlations. Bonferroni correction for multiple measures was applied for all analyses.

Receiver operating characteristic (ROC) curve analyses were performed to evaluate the discriminating power of FCSRT scores and clinical diagnosis. The area under the curve was used as a measure of the overall performance of each test (with a 95% confidence interval). Moreover, we assessed whether the area under the curve values were significantly different using a nonparametric method for correlated samples (Delong's method). Optimal cutoff points for the FCSRT were calculated by selecting the point on the ROC curve that maximized both sensitivity and specificity. In addition to the ROC curve analyses, a logistic stepwise regression analysis (using the Enter method) was carried out after selecting FCSRT scores with the least overlap between groups.