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Pure progressive amnesia: An atypical amnestic syndrome?

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We report on M.S., an 83-year-old patient with isolated pure progressive amnesia. This rare, recently identified, form of amnesia has been described in elderly patients. Neuropathological studies suggest that this syndrome is an atypical clinical presentation of Alzheimer's disease. The aim of our study was to characterize the neuropsychological pattern of pure progressive amnesia in comparison with other amnestic syndromes and memory dissociations reported in the literature. Our results indicate that pure progressive amnesia is characterized by a highly unusual dissociation in the realm of memory, with severe deficits on tests based on recognition and recall of verbal and visual single items, contrasting with relatively preserved anterograde autobiographical and spatial memory and normal recall of complex material such as stories. These findings suggest that memory for single items could depend on an independent system. One hypothesis is that M.S.'s unusual memory profile results from relative dysfunction of the ventral medial temporal lobe pathway. An alternative explanation implicates cognitive reserve. Further studies are required in order to progress on this matter. In any case, pure progressive amnesia is a clinical syndrome that may provide further insight into the organization of declarative memory.

INTRODUCTION

A wide variety of amnestic syndromes in relation to various pathological conditions and anatomical substrates have been described (see Kopelman, 2002, for a review). The characterization of these syndromes has considerably improved the understanding of how memory is organized in the human brain. Several dissociations following medial temporal lobe damage have been reported. For example, a dissociation between impaired episodic and preserved semantic memory has been

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described in three adolescents who suffered from hippocampal damage (Vargha-Khadem et al., 1997). The adolescents showed impaired spatial, temporal, and autobiographical memory that significantly restricted their independence. Despite their severe amnesia, they were able to attend regular school and acquire a substantial amount of factual knowledge. It was further demonstrated that one of the three adolescents, Jon, was able to acquire a significant amount of knowledge about previously unknown events through repetition (Baddeley, Vargha-Khadem, & Mishkin, 2001). These studies indicated that acquisition of semantic memory could sometimes be preserved despite severely impaired episodic memory, at least in the context of developmental amnesia.

Another dissociation, between impaired recollection and preserved familiarity, has been reported with convincing evidence. The three adolescents mentioned above obtained normal scores on tests assessing verbal and visual recognition memory. Additional investigations with Jon showed that he could recognize previously learned items despite poor recollection of the context in which the items were learned (Baddeley et al., 2001). It was suggested that Jon performed well on recognition tasks because he could rely on familiarity. A growing number of single case and group studies of adults who became amnesic during adulthood have reported a similar dissociation, suggesting that familiarity and recollection could be independent processes (Aggleton et al., 2005; Barbeau et al., 2005a; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Yonelinas et al., 2002).

Patients with medial temporal lobe dysfunction caused by degenerative lesions can equally give insight into the organization of memory. Several elderly patients with severe isolated amnestic syndromes of insidious onset and gradual progression, contrasting with preserved autonomy, have been reported (Caffara & Venneri, 1996; Caselli, Couce, Osborne, Deen, & Parisi, 1998; Didic, Ali Cherif, Gambarelli, Poncet, & Boudouresques, 1998; Kritchevsky & Squire, 1993; Lucchelli, De Renzi, Perani, & Fazio, 1994; Miceli et al., 1996; Stokholm, Jakobsen, Czarna, Mortensen, & Waldemar, 2005). This syndrome, which we refer to as pure progressive amnesia, is thought to result from medial temporal lobe dysfunction (Butters, Lopez, & Becker, 1996; Lucchelli et al., 1994). It is characterized by a severe amnestic syndrome of insidious onset, with memory performance that can remain stable or decline slowly over several years. Across this period of time, other cognitive domains remain preserved, as well as independence regarding most aspects of daily life. However, all patients for which follow-up data were available have slowly progressed towards dementia. In two cases, neuropathological hallmarks of Alzheimer's disease (AD) have been found (Caselli et al., 1998; Didic et al., 1998). Pure progressive amnesia may therefore represent a rare clinical presentation of AD, characterized by a focal isolated memory deficit over a prolonged period of time. In-depth investigation of this amnestic syndrome has never been conducted, presumably because this syndrome is rare and can easily be confounded with the classical form of AD. In the present paper, we describe the neuropsychological profile of a patient with pure progressive amnesia in detail and report an unusual dissociation within the realm of memory.

We report on M.S., a patient with a pure progressive amnestic syndrome of insidious onset and gradual worsening. This case-study revealed an unusual pattern of amnesia, unlike those reported in the literature, with a dissociation between impaired single-item and preserved complex material memory acquisition. M.S. was severely impaired on all tasks requiring recall and recognition of verbal and visual single items, while anterograde semantic, autobiographical, and spatial memory were relatively intact.

CASE DESCRIPTION

M.S. was first examined in our memory clinic in March 2002, at the age of 83. He had received 17 years of formal education and had graduated in law. A successful politician during most of his career, he had, for example, been elected to the

French senate and held appointments to several international organizations. His memory problems started gradually at the age of 79 (1998). He first consulted a neurologist in April 2001. On examination, there was an isolated memory impairment, as well as symptoms of mild depression, which quickly resolved with a serotonin reuptake inhibitor. He was then referred to our memory clinic for further evaluation. All experimental data reported thereafter were collected 18–24 months after this initial depression.

When first examined in our department, he was complaining of forgetfulness of insidious onset that had slowly worsened over time. He reported losing his personal belongings and missing appointments. He also had increasing difficulties playing bridge because he forgot previous announcements. M.S. was fully independent, was involved in various social committees, and exercised on a daily basis. As an example, he regularly went mountain climbing and skiing until July 2002. A cheerful, witty man, very eager to understand his memory problems, he enjoyed recalling various trips around the world during his political career, which were recalled in great detail.

When examined on several occasions in March 2002 and September 2002, as well as in April 2003, he always came to his appointments by himself. Elementary neurological examination was unremarkable. Sight and hearing were found to be normal. He did not drink or smoke. His personal medical history included an angioplasty for coronary artery disease. No family history of neurological disease was identified, but both his parents died before the age of 65. A complete haematological and biochemical screening was within normal limits (full blood cell count, thyroid, liver, and renal function tests, serum glucose, electrolytes, serum protein electrophoresis, sedimentation rate, B9 and B12 vitamin levels, serology for syphilis). An electroencephalogram (EEG), recorded on two occasions, was also normal.

General neuropsychological assessment

M.S.'s IQ was above average (global IQ = 114; 82nd percentile). He obtained high scores on all subtests of the WAIS-III (Wechsler Adult Intelligence Scale; Wechsler, 2000), and there was no difference between his verbal and performance IQ. Working memory, executive functions, language, praxis, and visuo-perceptive skills were all normal (results summarized in Table 1). These preserved abilities contrasted with a severe deficit in the realm of memory. His general delayed memory score on the WMS-III (Wechsler Memory Scale; Wechsler, 2001) was 75 (5th percentile).

It is noteworthy that M.S.'s performance on the auditory recognition index of the WMS-III was at the 0.5-percentile level. Concerning subtests of the WMS-III, it should be noted that the use of scaled scores can hide valuable information for elderly people, presumably due to large standard deviations in the control group (Collie & Maruff, 2000). For example, although M.S. did not recall a single item of the delayed verbal paired-associates subtest, he obtained a scaled score of 5. He also obtained a scaled score of 7 on the delayed face subtest, although his performance was at the level of chance (raw score = 26/48, chance = 24/48).

His memory impairment appeared equally on the Free and Cued Selective Reminding Test (FCSR; Grober, Buschke, Crystal, Bang, & Dresner, 1988; French adaptation: Ergis, Van der Linden, & Deweer, 1994). In the FCSR, recall is first assessed through free recall and then using cues for the words that have not been retrieved. This procedure, repeated three times in order to give the subject the opportunity to improve his performance (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994), is followed by a recognition subtest as well as delayed recall. Despite reinforced encoding, M.S. was found to be severely impaired on the FCSR. His performance, both on delayed recall and on the recognition subtest, was 8 standard deviations below the mean for control subjects (Table 2).

M.S. also underwent the DMS48, a visual recognition memory test (Barbeau et al., 2004). This test includes 48 targets, each target being shown simultaneously with a distractor during the recognition procedure. Targets are equally

Table 1. *M.S.'s results on the standard neuropsychological assessment*

Test	*Result*
Intelligence scale (WAIS-III)[a]	
Vocabulary	16
Similarities	12
Arithmetic	10
Digit span	11
Information	13
Comprehension	13
Picture completion	12
Digit symbol-coding	12
Block design	12
Matrix reasoning	12
Picture arrangement	9
Verbal IQ	116 (86th percentile)
Performance IQ	109 (73rd percentile)
Full scale IQ	114 (82nd percentile)
Memory scale (WMS-III)[a]	
Logical memory I	10
Logical memory II	10
Face recognition I	8
Face recognition II	7
Verbal paired associates I	6
Verbal paired associates II	5
Family pictures I	8
Family pictures II	7
General delayed memory	75 (5th percentile)
Executive functioning	
Trail Making Test A	51 s (60 ± 26)
Trail Making Test B	226 s (152 ± 83)
Copy of the Rey Osterreich figure	36/36 Type 1, 4 mn 08 (50th percentile)
Word fluency "animals" in 2 mn	35 (29.7 ± 11.9)
Word fluency "p" in 2 mn	30 (20.8 ± 7.3)
Stroop test	Normal
Frontal assessment battery	17/18 (17.3 ± 0.8)
Language	
Picture naming	79/80 (cut-off = 69)
Pyramid–Palm Trees Test (visual)	48/52 (cut-off = 49)
Visual abilities	
Benton face perception	49 (41–54)
Benton line orientation	28 (25.7)
Praxis	29/29

Note: Norms are presented in parentheses. WAIS = Wechsler Adult Intelligence Scale. WMS = Wechsler Memory Scale.
[a]Scaled scores: m = 10 ± 3.

Table 2. *M.S.'s performance on the Free and Cued Selective Reminding Test*

	Score				
		April 2001		*April 2003*	
	Max.	*Score*	*Z*-score	*Score*	*Z*-score
Total recall (free + cued) immediate recall	48	35	−4.1	21	−9.2
Free delayed recall	16	4	−2.5	0	−3.9
Total (free + cued) delayed recall	16	10	−6.3	5	−12.2
Recognition	48	43	−6.1	41	−8.8

Note: Results show progressive worsening of M.S.'s memory impairment.

presented on either the left or the right side of the page. The participant is asked to identify the target that has been previously presented, if necessary using forced-choice recognition. This test is easy for control subjects who make on average no more than three errors. Yet M.S. performed −5.8 and −9.3 standard deviations (23 errors) below controls' mean on immediate and delayed recognition, respectively, performing only slightly above chance.

M.S.'s performance on the FCSR and the DMS48 could not be explained by poor verbal abilities or visual dysfunction. He obtained nearly perfect scores on a picture-naming task, performing at normal speed (Deloche & Hannequin, 1997). Propositional language and comprehension were flawless. He performed above average on a visuo-perceptual task that requires matching unknown faces (Benton, Sirvan, De Hamsher, Varney, & Spreen, 1983b), as well as on a visuo-spatial task (Benton, De Hamsher, Varney, & Spreen, 1983a). His performance was also normal on the Visual Object and Space Perception battery (VOSP; Warrington & James, 2000), with the exception of the silhouette subtest (−2.1 standard deviations below mean).

In comparison with the first neuropsychological assessment in May 2001, M.S. obtained identical or better scores on all executive function tests in

April 2003 (for example, he was able to provide the name of 20 animals and 27 words beginning with letter "P" in 2001 compared to 30 animals and 35 words in 2003; his digit span was 5 forward and 4 backward in 2001, and 6 forward and 4 backward in 2003). These results may be explained by his positive response to the treatment of his slight initial depression. At the same time, memory performance worsened, as shown by the scores at the FCSR in 2001 and 2003 (Table 2).

In summary, preliminary neuropsychological data revealed an isolated anterograde amnesia of insidious onset and progressive worsening. It is generally considered that a score is impaired if it is 2 standard deviations below controls' mean. It has to be noted that M.S.'s delayed MQ (75) did not reach that criterion (−1.67 standard deviations). However, his global IQ was of 1 standard deviation above mean (114), and the difference between global IQ and delayed QM was found to be statistically significant ($p < .01$, WMS-III statistical manual). M.S.'s memory impairment could be considered as severe, since he performed well below 2 standard deviations on both the FCSR and the DMS48, suggesting marked difficulties to process the kind of information used in these tests. Both tests are thought to be relatively independent from executive functioning and sensitive to medial temporal lobe dysfunction (Barbeau et al., 2004; Petersen et al., 1994; Pillon et al., 1994). It is therefore plausible that M.S.'s amnesia resulted from medial temporal lobe (MTL) dysfunction.

However, despite poor performance on standard memory assessment, several intriguing features were observed during his stay as an inpatient at the hospital. First, unlike other amnesic patients, he seemed to have no difficulty recalling what he had done during the previous days, such as the different examinations he had undergone, or the various members of the staff he had met. Thus, some aspects of anterograde autobiographical memory appeared to be preserved. Secondly, he had no difficulty finding his way in the hospital (in contrast to many healthy visitors and out-patients) suggesting a preserved ability to remember new routes and locations. Finally, his recall of complex material seemed to be more accurate than his ability to recall single items. For example, he obtained a normal scaled score on the logical memory subtest of the WMS-III, which is based on the free recall of two complex stories (scaled score of 10 on immediate recall and of 10 on delayed recall; $M = 10$, $SD = 3$). A similar result was observed with the Rey–Osterrieth complex figure. M.S. obtained normal scores at both immediate recall (score = 9; $M = 14.5$, $SD = 6.3$) and after a 30-min delay (score = 13; $M = 13.8$, $SD = 6.1$). These results contrast with all scores obtained on single stimuli-based tasks such as the FCSR, the DMS48, the verbal delayed paired associates, or the face recognition tests. With these questions in mind and M.S.'s informed consent, further evaluation was undertaken with the aim to inquire for possible dissociations.

Assessment of item recognition memory

M.S. underwent a battery of 11 recognition memory tests using single stimuli developed in our laboratory. Despite a large variety of stimuli (words, faces, fruits, vegetables, abstract shapes) and procedures (forced-choice or yes/no responses), M.S.'s performance was found to be consistently impaired (Figure 1). On average, his performance was at −6.9 standard deviations ($SD = 4.0$) below the mean of controls (mean age = 79.3, $SD = 2.2$). Level of chance for 8 of the 11 tests was 50% (one distractor for one target; the level of chance for the three other tests was 44, 33, and 25%). Performance of control subjects always remained well above the level of chance (the minimum difference between level of chance and performance on any of the tests for all control subjects being 20%), suggesting that these tasks were on the whole relatively easy as there was no floor effect.

Furthermore, M.S. performed below 10 standard deviations on three tests. In the forced-choice (FC) verbal test, participants have to learn a series of 48 words and recognize them after a delay of 3 and 60 minutes. M.S.'s *Z*-score after the 3-minute delay was −3.3 but dropped

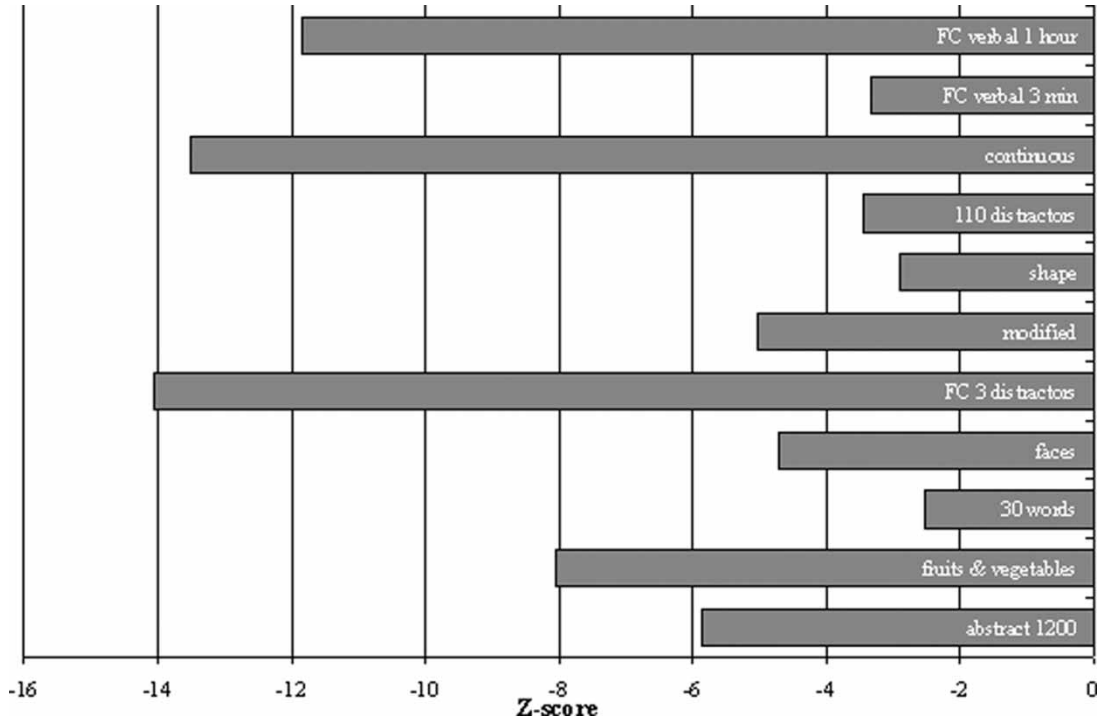

Figure 1. *M.S.'s Z-scores on 11 laboratory recognition memory tasks. M.S. performed below cut-off score (− 2 standard deviations below mean) on all tests. FC = forced-choice procedure, otherwise yes/no format.*

to −11.8 after 1 hour, answering exactly at random at that moment. This suggests not only that M.S. had difficulties encoding and storing verbal information in memory for a short delay (3 minutes), but that even the little information that he had encoded was forgotten in the following hour. He also failed on a continuous recognition task (−18.4 standard deviations) in which participants watch a series of pictures during 10 minutes and have to say for each picture whether it had already been presented in the series or not. This task requires deciding simultaneously whether each picture has been seen or not and, if not, encoding it for the eventuality that it becomes a target later in the series. M.S. also failed on a task (−14.0 standard deviations) in which each target has to be found among three distractors (FC 3 distractors) after a 2-minute delay. Thus on the whole, manipulation of any variable of the recognition tasks that made the task more difficult (longer delay before recognition, simultaneous recognition/encoding operations, recognition among different distractors) affected M.S.'s performance to a disproportionate extent relative to controls.

Assessment of autobiographical memory

M.S.'s autobiographical memory was assessed with a standardized test, designed to measure autonoetic recall (Piolino et al., 2003). Participants are asked to provide a detailed description of specific events that have occurred during their life. They have to recall four events covering five major periods of their lifespan. M.S. obtained normal scores for all of the five periods (Figure 2). He notably obtained a normal score concerning the previous year, suggesting preservation of autobiographical memory for events that had occurred after the onset of his memory disorder.

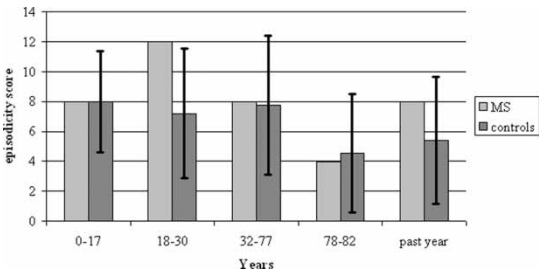

Figure 2. *M.S.'s performance on a standard test of autobiographical memory (TEMPau). He obtained normal performance concerning all periods, including the last period (after presumable disease onset). Vertical lines represent standard deviations.*

His ability to recall autobiographical events was further evaluated in an ecological setting. M.S. was accompanied on a 30-minute walk through the hospital. After a 24-hour delay, he was asked to verbally recall this episode and all the events that had occurred during the walk. He had no difficulty providing a detailed report. This is a literal translation of his spontaneous account: "We went to have a drink on the ground floor, but we had to wait a long time for the elevator. She [the examiner] went to buy Le Point [a magazine], but I did not buy anything myself. We then drank a hot chocolate in the small café, which is near the entrance. We afterwards went to the children's hospital, which we visited for some time and from where we saw the helicopter platform. Then we came back." All episodes were correctly recalled with the exception of the episode concerning the purchase of the magazine. He, not the examiner, bought the magazine on the examiner's request.

Assessment of semantic memory

M.S.'s scaled-score on the information subtest of the WAIS-III (which assesses general, cultural knowledge about the world) was 1 standard deviation above mean. He also underwent a questionnaire that assesses knowledge usually acquired through school, designed for patients of his age group. His score was perfect (20/20) for both the historical ($M = 16.6$, $SD = 4.0$) and geographical ($M = 18.8$, $SD = 2.2$) parts of the test. When shown the names of famous people, he was able to provide detailed information on 9/10 people (he failed concerning a young popstar; score = 9, $M = 8.8$, $SD = 1.2$). He was also shown a series of photographs of famous people and was asked to provide the name, or alternatively as many biographical details about the person as possible. M.S. could only name 20 out of 40 faces ($M = 34.6$, $SD = 5.4$) and provided verbal details on only 8 out of the remaining 20 faces (total = 28, $M = 38.0$, $SD = 2.4$), performing lower than 23 control subjects matched for age. He was then shown a series of 10 photographs of famous events. His performance did not differ from that of control subjects (83%, $M = 87.8\%$, $SD = 5.9\%$). Notably, he obtained a perfect score on all three events that happened after the onset of his memory problems. Finally, he was asked to recall public events that had occurred after the onset of his memory disorder (year 2001). He was spontaneously able to provide an accurate account of 14 events covering the major highlights in politics and sporting events of this period.

Assessment of spatial memory

Route learning in a real environment

Methods. In order to evaluate to which extent spatial memory was preserved in M.S., we designed a route-learning test in which M.S. and normal controls had to learn two circuits in the hospital (mean length: 267 m, $SD = 32$). The first route had 15 decision points (locations where participants have to make a decision whether to turn right, turn left, or continue straight on), and the second had 13. Each itinerary was completed in about 5 minutes. Participants were shown the route once before the evaluation began. During the evaluation, each error was corrected. Trials were repeated until two consecutive trials were successfully performed. After a 1-hour delayed trial, participants were asked (a) to point in the direction of three decision points (point of departure, the nurse's office, the library), (b) to complete the same itinerary in the reverse way, (c) to draw the two routes on a floor map, and (d) to verbally provide a detailed description of each route.

Results. M.S. perfectly succeeded on all of these tasks (Figure 3). He could point to all directions without hesitation. He made no error when completing the routes in the opposite direction and successfully drew paths on the map (Figure 4). His verbal recall suggested that he was able to imagine himself walking on the path. M.S. was asked to complete the first path 8 months after he had learned it. He remembered it without hesitation and made only one error out of 15 decision points.

Route learning in a virtual environment

M.S. may have been familiar with the environment of our previous experiment as an in-patient. In order to control for this effect, a virtual spatial task was designed.

Methods. The itinerary was video-recorded from the front of a car driving through the suburb of a town from the perspective of the driver. The town was unknown to all participants. The video was shown on two occasions, since older participants could be unfamiliar with this type of procedure. The length of the itinerary was about 4 kilometres; it lasted for 6 minutes and contained 15 decision points. At each intersection, the participant had to decide whether the car had to turn right, turn left, or continue straight ahead. Performance was assessed in three consecutive trials. In addition, M.S. performed a trial after a 24-hour delay.

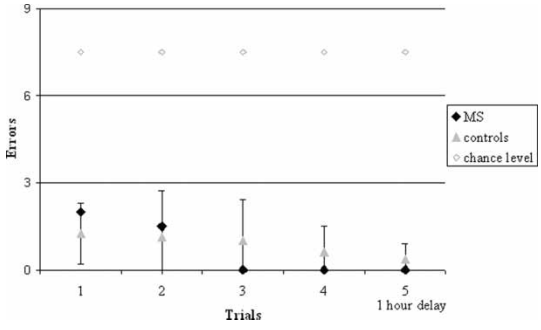

Figure 3. *M.S.'s performance on two routes learning tests in a real setting. His performance was normal on all trials. Vertical lines represent standard deviations.*

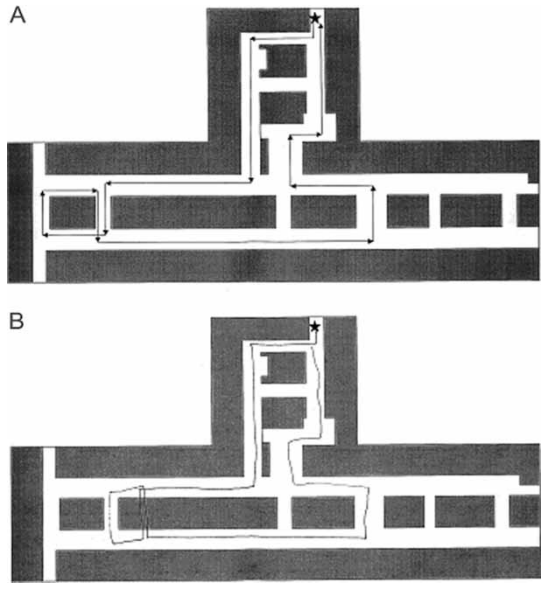

Figure 4. *A: Path Number 2. The star indicates the beginning and the return point of the path. B: M.S.'s drawing of the path on a blank map, indicating that he was able to recall the path he learned and to draw its abstract representation on a map.*

Results. M.S.'s performance improved at the same rate as that of controls and remained intact after a 24-hour delay (Figure 5).

Stylus maze

M.S. underwent the stylus maze test (Milner, 1972). Like previous spatial memory tasks, this

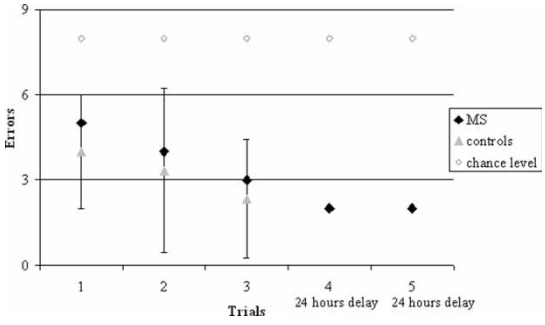

Figure 5. *M.S.'s performance on a virtual route learning test with 15 decision points. He obtained normal performance on all trials, with no loss after a 24-hour delay. Control subjects did not undergo the test at the 24-hour delay. Vertical lines represent standard deviations.*

task evaluates sequence learning, but in intrapersonal space. This task was chosen in reference to the case study of H.M., whose performance was consistently impaired (Milner, 1972).

Methods. Participants have to learn a path on a board covered by a matrix of 10 × 10 bolts. We used the same path that H.M. had to learn, which was made of 28 decision points. In order to reach criterion, the path has to be repeated with no error on three consecutive trials.

Results. M.S. learned the procedure after 23 trials, at a similar rate to that of control subjects (Table 3, controls from Milner, 1972). This is in sharp contrast with H.M., who never learned the task despite an impressive amount of trials (more than 215 trials). The same procedure was repeated at day +1 and day +2. M.S. consistently improved his performance (number of errors before reaching criterion at Day 0 = 158; at Day 1 = 70; at Day 3 = 13).

Brain imaging

Cerebral blood flow study

Methods. Acquisition of single photon emission computed tomography (SPECT) images was performed with a double-head gamma camera (DST; Sopha Medical Vision International) with fan-beam collimators. The images were acquired 1 hour after intravenous injection of 740 MBq ^{99m}Tc-ethylcysteinate dimer (ECD) with dimmed lights, in a quiet surrounding. The participant's head was safely positioned in an adjustable head folder. A total of 64 angular views of 60 s each were obtained through a 360° circular orbit. The data were recorded in a 128 × 128 matrix. SPECT images were then reconstructed from projection data using the filtered back-projection algorithm with a 0.30 cut-off frequency Butterworth filter and a software zoom of 2 (matrix, 128 × 128 × 128; voxel size, 1.7 × 1.7 × 1.7 mm). No attenuation correction was performed. Reconstructed brain slices were reoriented according to the bicommissural line.

A proportional Talairach's grid was semiautomatically drawn by Neurogam@ (SEGAMI@ Software), and 30 cortical regions of interest (ROIs) were defined on each hemisphere, using stereotactic coordinates of the Talairach and Tournoux atlas (Talairach & Tournoux, 1988), after segmentation. For each ROI, cerebral blood flow (CBF) was evaluated using a perfusion index calculated as the mean cortex-to-cerebellum ratio and also expressed in number of standard deviations compared to a reference population of 24 participants matched for age contained in the software. Perfusion was considered abnormal if it was more than 2 standard deviations below that of control subjects' mean.

Table 3. *M.S.'s performance on the stylus maze test*

	M.S.	*Controls*	*H.M.*
Number of trials to criterion	23	17.0	215 +
Number of errors to criterion	158	91.8	2,877 +

Note: Results show that M.S. performed at the level of controls and much better than H.M. Controls (younger in age than M.S.) and H.M. reported by Milner (1972).

Results. Using a cut-off value of −2.0 standard deviations below mean, there was marked hypoperfusion of the medial temporal lobes bilaterally, involving all hippocampal as well as subhippocampal structures predominating in the temporal lobes medially, extending to ventral and anterior temporal lobe regions (Table 4). Within medial temporal lobe structures, hypoperfusion predominated in the hippocampus (mean right and left *Z*-score: −4.40), very closely followed by the perirhinal (−4.10) and entorhinal cortices (−4.05). The subcallosal cortex showed hypoperfusion to a similar extent (−4.45). Hypoperfusion, to a lesser degree, was also observed in the posterior cingulate gyrus (−1.95) and in the occipito-temporo-parietal junction bilaterally (−2.30). Hypoperfusions were bilateral in all cases. The remaining areas within the temporal, frontal, parietal, and occipital cortex, as well as the thalami on both sides, showed normal perfusion (i.e., above cut-off).

Table 4. *SPECT results for M.S.*

	Z-score	
Region	*Left hemisphere*	*Right hemisphere*
Area 38 (occipito-temporo-parietal junction)	−2.1	−2.5
Area 23 (posterior cingulate)	−2.2	−1.7
Area 20 (anterior basal temporal lobe)	−2.9	−1.8
Area 36 (perirhinal cortex)	−4.8	−3.4
Area 28 (entorhinal cortex)	−4.3	−3.8
Area 25 (subcallosal cortex)	−4.3	−4.6
Hippocampus	−4.7	−4.1

Note: Results expressed in number of standard deviations below mean (*Z*-score). Hypoperfusion shown when more than 2.0 standard deviations below that of control subjects. The remaining brain areas were found to show perfusion above the cut-off of − 2.0 standard deviations.

Morphometric study with MRI

Images of M.S.'s brain were acquired with a 1.5 T Magnetom MRI (Siemens, Erlangen), using a standard head coil. It revealed diffuse and homogenous atrophy. The anterior temporal horns were enlarged, and medial temporal lobe structures were atrophied on both sides. T_2-weighted images showed punctuate foci of increased signal in the deep white matter of both hemispheres as well as in the putamen and the pallidum. No such lesions were observed in the thalami (with special attention brought to the anterior and mediodorsal nuclei), hippocampus, and parahippocampal gyrus.

Medial temporal lobes volumetry

Methods. A magnetization prepared rapid gradient recalled echo sequence allowing 3D reconstruction acquired in the sagittal plane, aligned on the axis of the hippocampus, and a tilted coronal gradient echo sequence was acquired on a 1.5 T Magnetom (TR = 1,320 ms, TE = 3.93 ms, TI = 800 ms, flip angle = 15°, FOV = 256 × 256, matrix = 256 × 256, slice thickness = 1.5). The images were reconstructed in the axial and coronal planes and reformatted to obtain 1-mm^3 isotropic voxels. Segmentation of the grey matter was manually performed on coronal sections perpendicular to the grand axis of the hippocampus. In order to measure the subregions of the medial temporal lobe, regions of interest based on specific anatomical landmarks were defined (Duvernoy, 1998; Insausti et al., 1998). They included the hippocampus (hippocampus proper, dentate gyrus and subicular complex) as well as entorhinal, perirhinal, and parahippocampal cortices. In order to control the effect of interindividual variability of participants' head size on the volumes of the studied structures, the volumes were normalized to the intracranial area (Eritaia et al., 2000). A total of 5 participants (mean age: 72.0 years, *SD* = 4.8) served as controls for this study. All underwent three tests of visual and two tests of verbal recognition memory, on which they obtained normal results.

Results. Detailed results are summarized in Table 5. Within the medial temporal lobe, atrophy predominated on the hippocampus when compared with results for control subjects (mean *Z*-score, left and right: −1.27), followed by perirhinal cortices (−0.93) and entorhinal cortices (−0.56). Volumes of the parahippocampal cortices did not differ from that of control subjects (−0.03).

DISCUSSION

Our case study of M.S., an 83-year-old patient with an amnestic syndrome and preserved overall intellectual efficiency, revealed a highly unusual dissociation in the realm of memory. M.S. failed on memory tasks for single items, such as recall of lists of words or recognition of verbal and visual items. In contrast, recall of complex material such as autobiographical and spatial memory was relatively preserved. Performance on formal memory tests based on complex relational material, such as words embedded in stories (WMS-III logical memory) and the recall of Rey's complex figure, was also preserved.

The comparison of two sets of tasks, one evaluating memory of single items, the other

Table 5. *M.S.'s medial temporal lobe volumetry*

		Controls		*M.S.*		
	Region	*Mean volume*[a]	*SD*	*Volume*[a]	*Percentage*	*Z–score*
Left	Hippocampus	2,936	593	2,230	76	−1.19
	Entorhinal	1,210	317	1151	95	−0.19
	Perirhinal	1,981	400	1,581	80	−1.00
	Parahippocampal	926	143	846	91	−0.56
Right	Hippocampus	3,175	612	2,357	74	−1.34
	Entorhinal	1,210	204	1,021	84	−0.93
	Perirhinal	2,007	620	1,478	74	−0.85
	Parahippocampal	932	238	1,051	113	+0.50

[a]In mm^3.

evaluating memory for complex material, revealed a significant difference ($p < .02$, Wilcoxon test, details in Table 6). Memory for single items was evaluated through recognition (11 tests from the recognition memory battery developed in our laboratory, the DMS48, the face subtest of the WMS-III), recall (the FCSR word list), and paired association (the paired-associate subtest of the WMS-III). Memory for complex material was assessed through autobiographical recall (TEMPau), spatial tasks (route learning; virtual route learning; maze task) as well as story and figure recall (WMS-III logical memory subtest; Rey's complex figure; WMS-III family pictures). This result was unexpected, since most tests for single items consist of recognition tests, which are easier than tests of recall. There was no ceiling effect for the tasks containing complex material, which could have explained this pattern. Also, there were no deficits in other areas of cognition that could explain M.S.'s poor performance on tests of single items. His level of verbal competence was high (in the high average), and he showed intact visuo-perceptive abilities. This was shown, for example, by his performance on the facial recognition test and on the VOSP. Attention and working memory was normal, as reflected by normal scores on various tests assessing these functions (e.g., digit span, Trail Making Test A and B). We therefore suggest that M.S.'s memory impairment is related to a major difficulty in encoding and/or storing single items, which then become unavailable through either recall or recognition, regardless of the sensory modality used.

This pattern of memory impairment is highly atypical and differs from previously reported amnestic syndromes. M.S.'s memory impairment differs from that observed in the three adolescents reported by Vargha-Khadem et al. (1997). M.S. showed relatively preserved autobiographical and spatial memory as well as independence, whereas these aspects were impaired in these young participants. On the other hand, M.S. consistently failed on all recognition memory tests (as well as on tests of recall of single items), while recognition was preserved in the adolescents. Also, the adolescents succeeded on paired-associate tasks, providing that the stimuli remained in the same modality (word–word or picture–picture associations), while M.S. failed on this type of task (e.g., performance on the WMS-III paired-associate subtest). However, semantic memory was relatively preserved in both M.S. and the adolescents. This fact therefore precludes a complete double dissociation between these types of amnesia. Furthermore, a dissociation between impaired recollection and preserved familiarity has been demonstrated in several studies. Yet such a dissociation is not likely to account for M.S.'s performance either. Although these aspects have not been evaluated in detail, it appears that neither familiarity nor recollection enabled him to recognize items. In summary, the pattern of dissociation observed in

Table 6. *Comparison of results on single-item and complex-material tests*

Test	*Results*
Single-item	
FC verbal 1 hr[a]	−11.84
FC verbal 3 min[a]	−3.33
Continuous[a]	−18.38
110 distractors[a]	−3.29
Shape[a]	−5.04
Modified[a]	−2.90
FC 3 distractors[a]	−14.05
Faces[a]	−4.70
30 words[a]	−2.51
Fruits & vegetables[a]	−8.06
Abstract 1200[a]	−5.85
DMS48	−9.30
WMS−III face subtest[b]	−1.00
FCSR word list	−8.80
WMS−III paired-associate subtest	−1.67
Mean	−6.7
SD	5.0
Complex-material	
TEMPau	0.61
Route learning	0.71
Virtual route learning	−0.32
Maze task	0.00
WMS−III logical memory subtest	0.00
Rey's figure	−0.13
Family pictures	−1.00
Mean	0.0
SD	0.6

Note: Performance on delayed tests when available. FC = forced choice. FCSR = Free and Cued Selective Reminding Test. WMS = Wechsler Memory Scale.

[a]Tests from the recognition memory battery. [b]Performance 1 standard deviation below mean but performed at the level of chance by M.S. (see General Neuropsychological Assessment section).

M.S. cannot easily be related to previously reported amnestic syndromes.

Single-item memory and models of declarative memory

By "single item", we refer to a concrete or abstract concept that is not embedded in a story (such as a word), or that is processed as an isolated or single part, such as a picture. The term *single item* is not very well defined in the literature on memory, although it is frequently used to refer to a single stimulus that has to be memorized (Cohen, Poldrack, & Eichenbaum, 1997; Henke et al., 1999; Mayes, Isaac, Holdstock, Hunkin, & Montaldi, 2001; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). In fact, a wide variety of memory tests in the animal and human literature are based on such material (e.g., visual recognition memory tasks, word lists). These tasks can be distinguished from those that require establishing conjunctions or relations among elements (such as stimulus association tests, configurational tests, object−place tests, place/time discontiguous events tests) or from those assessing context-rich memory such as spatial or autobiographical memory.

Eichenbaum and collaborators (Eichenbaum, 2000; Eichenbaum, Otto, & Cohen, 1994; Eichenbaum, Schoenbaum, Young, & Bunsey, 1996) have introduced a model of memory in which information is first memorized in an inflexible manner at the single-item level. This stage is also critical for paired-associate tasks within the same modality when the relation between the items is inflexible and can be stored as a single-item equivalent. In this model, it is thought that flexible relations between items are established in a subsequent stage, in particular when they are spatially or temporally discontiguous, or when transitivity across items is required (Wallenstein, Eichenbaum, & Hasselmo, 1998). Beyond their respective differences, other groups have elaborated similar hierarchical models of memory. Mishkin and collaborators have suggested that "context-free" memory such as recognition based on familiarity or semantic memory could be dissociated from "context-rich" memory such as memory for episodic events (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Mishkin, Vargha-Khadem, & Gadian, 1998). Aggleton and Brown (1999) also provide evidence for a distinction between two memory systems, one being crucial for familiarity judgements, while the other is thought to be critical for episodic and spatial memory. Although these models significantly differ in many aspects, all converge to the notion that memory for single items could be dissociated from memory for complex material

and context-rich episodes. In addition, these models converge concerning the involvement of critical brain structures for these stages: Item and context-free memory, as well as familiarity, are thought to depend on anterior subhippocampal areas (amongst which the perirhinal cortex plays a major role), while relational, context-rich memory is thought to depend on the hippocampal formation.

This perspective concerning declarative memory raises an intriguing issue. The hierarchical structure of these models suggests that impairment at the single-item level should interfere with the upstream acquisition of relational, context-rich information. However, the model of Mishkin and collaborators (Mishkin et al., 1997, 1998) indicates that there are two dissociable streams of information, one involved in single-item processing (the ventral pathway) and another involved in configurational and spatial processing (the dorsal pathway). According to this view, a dissociation between the impairment of one pathway and the preservation of the other would thus be possible. At the anatomical level, it has recently been argued that parallel cortical routes could relay sensory information to the hippocampus in the absence of the perirhinal cortex (Aggleton, Kyd, & Bilkey, 2004). Within this theoretical framework, M.S.'s performance may be explained by the preservation of a parallel route-processing memory for complex material.

Another intriguing issue is the status of semantic memory in M.S. Performance on most tests that evaluate semantic memory were within normal limits, when compared with controls of his age group, as demonstrated, for example, by his performance on the WAIS-III Information subtest (13; $M = 10$, $SD = 3$) and on other tests, including tests of anterograde semantic memory. Yet this is surprising as there is evidence to suggest that semantic memory depends upon similar systems that support single-item memory (Barbeau et al., 2005b; Davies, Graham, Xuereb, Williams, & Hodges, 2004). Therefore, should not both be impaired to a similar extent? Although M.S. obtained normal results on most tests assessing semantic memory, he failed on a famous face test, with a lower performance than that of 23 control subjects. Thompson, Graham, Patterson, Sahakian, and Hodges (2002) showed in a group of patients with questionable dementia of the Alzheimer's type (QDAT) that patients with an initial impairment on a famous-people test had a high risk to convert to DAT after a 1–2 years period. M.S.'s performance on a similar test may thus indicate evolution to a more widespread semantic impairment. Furthermore, M.S., as an intellectual and a previous high-level politician, probably had a particularly high level of premorbid semantic memory. It could thus be that semantic memory appears preserved in a comparison with patients of his age group, whereas it may show a significant decline compared to his personal premorbid level (thus demonstrating retrograde semantic loss). Although semantic memory is often referred to as context-free memory, this is only partially the case since any piece of new information on a given event is integrated in the previous knowledge that the participant already has about this event. For example, information on Lady Diana's death read in a newspaper will automatically be integrated with what we already know about her. Within this frame, M.S.'s semantic memory may appear preserved because most new pieces of information can be integrated in a previously acquired context that helps memorizing, whereas attempts to learn new single-item stimuli would meet with failure since they could not be related to any previous knowledge.

Pure progressive amnesia

The clinical features of M.S. are reminiscent of patients presenting with pure progressive amnesia. M.S. showed isolated amnesia, of gradual installation and worsening over the course of several years. No identifiable cause, such as tumour or significant vascular disease, was found to account for his memory loss.

The clinical pattern of M.S. resembles that of other patients with pure amnestic amnesia like, for example, T.T., who remained well oriented in time and space during a follow-up period of

8 years (Caffara & Venneri, 1996). Autobiographical memory, evaluated five years after the study onset, was still globally preserved. Like M.S., T.T. was severely impaired on the Buschke Selective Reminding Test (a word list memory test), as well as on paired-associate learning. A similar pattern of memory impairment was reported in the patient of Lucchelli et al. (1994). She was also well oriented in time and space and obtained a normal score on a maze-learning task. This contrasted with impaired performance on paired-associate learning and on face recognition tasks. A recent case-study of pure progressive amnesia with follow-up over a 8-year period had very similar features (Stokholm et al., 2005). Memory problems remained isolated until the last year when a more widespread impairment was observed. At the time of the first examination, the patient was already found to be severely impaired at word list learning and on recognition memory tasks (−2.8 standard deviations on the word part of the Recognition Memory Test). Memory performance on these tests slowly worsened over the years. Despite these severe deficits in a formal evaluation, he was reported to be independent in daily life. For example, during most of the follow-up period, he remained able to travel by himself, to shop for groceries, to continue gardening, and to take on small repair jobs in the house. From these ecological data, it is tempting to deduct that his spatial memory was globally preserved and that his memory difficulties did not significantly interfere with his daily life. Overall, all patients with pure progressive amnesia were described as independent, with no impairment in everyday activities (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001).

In previous reports on pure progressive amnesia, most of the discussion has focused on the pathological changes underlying the impairments. Although the possibility of ischaemic damage has been raised (Kritchevsky & Squire, 1993), a neurodegenerative condition seems more likely to be the origin of this disorder. Two patients who had suffered from a long-standing isolated memory impairment ultimately progressed to a pattern of cognitive deterioration meeting the criteria for Alzheimer's disease (Squire & Kritchevsky, 1996). In two other patients who came to autopsy, neuropathological data showed widespread Alzheimer-type changes (Caselli et al., 1998; Didic et al., 1998). In addition, group studies have identified pure progressive amnesia as a distinct and rare clinical variant of Alzheimer's disease (Butters et al., 1996). Such a severe and isolated memory loss has been estimated to occur in about 3% of patients with a newly recognized cognitive impairment (Bowen, Teri, Kukull, McCormick, McCurry, & Larson, 1997). Taken together, these data suggest that pure progressive amnesia may represent an atypical presentation of Alzheimer's disease.

The neural substrate of M.S.'s memory impairment: Hypotheses

Based on M.S.'s clinical features, Alzheimer's disease with a highly unusual clinical course is the most likely pathological substrate of M.S.'s condition. Other conditions such as encephalitis, seizures, Korsakoff's syndrome, paraneoplastic disorders, transient global amnesia, and tumour are unlikely to account for his memory impairment. Periventricular signal hyperintensities on T2-weighted magnetic resonance imaging (MRI), such as those found in our patient, deserve some consideration. Chronic ischaemic injury could have damaged brain areas that are crucial for memory, such as the hippocampus or the anterior and dorso-medial thalamic nuclei (Aggleton & Brown, 1999). However, a neuroimaging study on M.S. revealed no evidence of vascular damage in these structures.

In Alzheimer's disease, neurofibrillary tangles (NFT) emerge in the ento- and perirhinal cortex stages (I and II) before spreading to the hippocampus (Braak & Braak, 1991). The subsequent stages (III and IV) are characterized by severe destruction of the rhinal cortices and spreading to the hippocampal formation. It is tempting to suggest that M.S.'s memory disorder may represent an atypical clinical correlate of Stage II/III of Braak and Braak's classification. In a previous section, we referred to models of declarative

memory, which postulate that item and context-free memory, as well as familiarity, depend on anterior subhippocampal structures, while relational context-rich memory depends on the hippocampal formation. In this line of thought, relatively circumscribed medial temporal lobe lesions to rhinal cortices could explain M.S.'s unusual pattern of amnestic syndrome and in particular its relative specificity to single-item memory. In line with the hypothesis that rhinal cortices could be impaired in isolation, the clinical data clearly suggest residual function of the hippocampus in M.S. Unlike amnesic patients with hippocampal damage (e.g., Vargha-Khadem et al., 1997), anterograde autobiographical and spatial memory was spared in M.S., suggesting that M.S.'s hippocampi were still partially functional. Furthermore, M.S.'s preserved ability to draw maps of routes that he had just learned is incompatible with complete hippocampal dysfunction.

However, this hypothesis remains speculative. Brain volumetry performed in M.S. did not support this interpretation, showing atrophy in both anterior subhippocampal and hippocampal structures. A similar pattern of hypoperfusion was found on SPECT.

A tempting explanation to conciliate clinical and anatomical data would be to hypothesize that M.S.'s memory deficit for single items results from damage of the ventral MLT pathway involving the perirhinal cortex and the hippocampus. Conversely, M.S.'s preserved abilities to solve spatial memory tasks could suggest sparing of the dorsal MTL pathway (Epstein, Harris, Stanley, & Kanwisher, 1999; Habib & Sirigu, 1987; Parkinson, Murray, & Mishkin, 1988). This is supported by the relative preservation of the posterior parahippocampal gyrus by volumetry (Z-score $= -0.03$) and SPECT (the hippocampus and anterior subhippocampal structures showed hypoperfusion around -4.0 standard deviations whereas the posterior parahippocampal gyrus was above the cut-off score of -2.0 standard deviations). Anatomical studies have also shown direct connections from parietal and frontal lobes to the hippocampus (Goldman-Rakic, Selemon, & Schwartz, 1984; Seltzer & Van Hoesen, 1979). These functional networks may support spatial and autobiographical memory in M.S. Further anatomical and functional imaging studies are required to solve this issue.

An alternative hypothesis is based on the concept of cognitive reserve. M.S. had a relatively high IQ (114), as have most patients with pure progressive amnesia ($M = 115.0$, $SD = 11.7$ for the 5 patients in whom IQ was provided; Caffara & Venneri, 1996; Didic et al., 1998; Kritchevsky & Squire, 1993; Lucchelli et al., 1994; Stokholm, et al., 2005). The concept of cognitive reserve suggests that nonacquired variables (e.g., larger head size, greater neuronal density) and life experience (e.g., high educational and occupational achievement) may provide a buffer against brain dysfunction when confronted with acquired central nervous system dysfunction (Legendre, Stern, Solomon, Furman, & Smith, 2003). It is possible that M.S. benefited from cognitive reserve in such a way that most cognitive domains were clinically preserved, although the disease process was more widespread. Relational context-rich memories may rely on wider cortical networks than those for single-item memory, which may depend on a specific module (Cohen et al., 1997). Within this context, the patient may also have undergone extensive reorganization of function, in favour of compensatory mechanisms at an advanced age.

In summary, M.S.'s memory impairment is probably related to an atypical course of Alzheimer's disease, leading to an unusual pattern of memory impairment. In this context, we propose two hypotheses, not mutually exclusive, that can account for this pattern of memory impairment. One focuses on the initial site of NFT lesions beginning in subhippocampal structures leading to dysfunction of the ventral MTL route. The other focuses on cognitive reserve. However, further studies are required to make progress on this matter.

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