

Autobiographical memory and auto-noetic consciousness: triple dissociation in neurodegenerative diseases

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Summary

Few studies have investigated autobiographical amnesia in neurodegenerative diseases and yet these pathologies are particularly relevant when addressing the issue of theories of long-term memory consolidation. According to the standard model, the medial temporal lobe (MTL) is involved in the storage and retrieval of episodic and semantic memories during a limited period of years. An alternative model, the multiple trace theory (MTT), suggests that the capacity of the MTL to recollect episodic memories is of a more permanent nature. In order to test these models, we studied three groups of patients with a neurodegenerative disease predominantly affecting different cerebral structures namely the MTL (13 patients in the early stages of Alzheimer's disease) and the neocortex involving either the anterior temporal lobe (10 patients with semantic dementia) or the frontal lobe (15 patients with the frontal variant of frontotemporal dementia, fv-FTD). We compared these groups of patients with control subjects using an original and reliable autobiographical memory task designed specially to assess strictly episodic memory over the entire lifespan. This task, developed on the basis of the most up-to-date definition of episodic memory, takes into account the ability to mentally travel back in time and re-experience the source of acquisition (remembering, i.e. auto-noetic consciousness) via the remember/know paradigm. All three groups of patients produced strongly contrasting profiles of auto-

biographical amnesia (regardless of the nature of the memories), which also differed markedly from that of the control group: temporally graded memory loss in Alzheimer's disease, showing that remote memories are better preserved than recent ones; memory loss with a reversed gradient in semantic dementia; and memory loss without any clear gradient in fv-FTD. Most strictly episodic memories (i.e. unique, specific in time and space, and detailed) were impaired, whatever the time interval considered in the three groups, though the memory loss was ungraded in Alzheimer's disease and fv-FTD, and temporally graded in semantic dementia, sparing the most recent period. A deficit of auto-noetic consciousness emerged in Alzheimer's disease and fv-FTD, but not in semantic dementia, though beyond the most recent 12-month period, the latter group could not justify their subjective sense of remembering to the same extent as the controls, in terms of the actual contextual information retrieved—phenomenological, spatial or temporal details. Our results demonstrate that autobiographical amnesia varies according to the nature of the memories under consideration and the locus of cerebral dysfunction. They are discussed in the light of the two competing models of long-term memory consolidation and recent conceptions of autobiographical recollection: new insights based on current concepts of episodic memories challenge the standard model and tend to support the MTT instead.

Keywords: episodic memory; Alzheimer's disease; semantic dementia; frontotemporal dementia; consolidation

Abbreviations: AM = overall autobiographical memory score; EM = strictly episodic memory score; fv-FTD = frontal variant of frontotemporal dementia; MMSE = mini-mental state examination; MTL = medial temporal lobe; MTT = multiple trace theory; R = remember; R/K = remember/know

Introduction

The difficulty of acquiring new information (anterograde amnesia) has been investigated more thoroughly than the difficulty of retrieving remote information. Retrograde amnesia refers to the loss of memory for information acquired before the onset of the cerebral pathology. Different profiles of retrograde amnesia have been identified, notably with regard to autobiographical memory, based on the locus of the lesion and the nature of the information being considered, thus revealing the complexity of deficits of remote memory (for reviews see Kapur, 1999; Conway and Fthenaki, 2000; Kopelman and Kapur, 2001; Kopelman, 2000a, 2002). Remote autobiographical memory has been examined in amnesic syndromes (Kopelman *et al.*, 1999), as well as in neurodegenerative diseases. In Alzheimer's disease in particular, a pattern of retrograde amnesia has been found which obeys Ribot's Law (Ribot, 1881), old memories being better preserved than recent ones (Kopelman, 1992; Greene *et al.*, 1995; Leplow *et al.*, 1997). Only a few controlled studies have been carried out on autobiographical memory in the temporal or frontal variants of frontotemporal dementia (Neary *et al.*, 1998; Hodges *et al.*, 1999). The temporal variant of frontotemporal dementia (Edwards-Lee *et al.*, 1997; Hodges *et al.*, 1999) corresponds to semantic dementia, which involves semantic disorders arising from an atrophy of the polar and inferolateral regions of the temporal lobe (Hodges *et al.*, 1992), with relative sparing of the medial temporal lobe (MTL), at least in the early stages (Galton *et al.*, 2001). Thus, semantic dementia is characterized by a neuropsychological and neuroanatomical profile of damage that is the mirror image of the amnesic syndrome profile, i.e. disorders of episodic memory and lesions of the MTL and surrounding structures. The frontal variant of frontotemporal dementia (fv-FTD) is characterized by behavioural changes and executive deficits related to predominant frontal lobe atrophy.

Clinical findings in semantic dementia and fv-FTD have often highlighted the preservation of day-to-day memory (Neary *et al.*, 1998; Murre *et al.*, 2001) and suggested that autobiographical memory, which refers to events and information about personal life that ensure continuity and a sense of identity, may also be spared. Some neuropsychological investigations, however, involving either single case or group studies, have reported the presence of autobiographical amnesia, though with differing profiles, according to the pathology. Indeed, some authors have shown that recent memories are remembered better than more distant memories in semantic dementia (Snowden *et al.*, 1996; Graham and Hodges, 1997; Piolino *et al.*, 2003; for a review see Hodges and Graham, 2001), while others have failed to find evidence of any similar time effect in fv-FTD (Hodges and Gurd, 1994; Thomas-Antérion *et al.*, 2000). Recently, Nestor *et al.* (2002), comparing patients with semantic dementia and fv-FTD by means of the autobiographical memory interview (Kopelman *et al.*, 1989), demonstrated a step-like time effect in the

semantic dementia group and no significant temporal gradient in the fv-FTD group. Such profiles suggest that differential mechanisms may be at the root of autobiographical memory impairment in semantic dementia and fv-FTD: the loss of autobiographical memory in semantic dementia, where semantic memory is affected, may be attributable to a deficit of stored information (Graham and Hodges, 1997), while the difficulty of retrieving autobiographical memory regardless of the time period in fv-FTD may reflect a deficit of strategic processes due to frontal/executive dysfunction (Thomas-Antérion *et al.*, 2000).

Nevertheless, the issue of temporal gradient and the nature of remote autobiographical memory impairment remains controversial in dementias displaying more complex and variable patterns. In Alzheimer's disease, for instance, a temporal gradient is not always found (see Nestor *et al.*, 2002). Similarly, in several single-case studies, the authors have reported a relatively well-preserved memory for autobiographical episodes in semantic dementia, regardless of the time period being tested (Kitchener and Hodges, 1999; Moss *et al.*, 2000; Westmacott *et al.*, 2001; Piolino *et al.*, 2003), in apparent contradiction with previous studies. As far as patients with fv-FTD are concerned, Graham (1999) notes that in the case reported by Hodges and Gurd (1994), six of the 10 memories recalled came from the subject's early life (1930s and 1940s). Nestor *et al.* (2002) have also provided evidence, using the Crovitz method, that these patients produce more truly specific memories from the first three decades of life than from the year prior to the testing, unlike those suffering from semantic dementia. Moreover, the level of impairment relative to controls differs from study to study (Thomas-Antérion *et al.*, 2000; Nestor *et al.*, 2002). Such discrepancies between investigations may be related to patient selection, depending on the stage of their disease and their degree of atrophy, particularly whether it occurs unilaterally or bilaterally.

The profile of autobiographical impairment may also depend on the definition of autobiographical memory that is applied. Based on the first definition of episodic memory (Tulving, 1972, 1983), autobiographical memory has been regarded as episodic in nature. Autobiographical memory, however, is a complex concept which implies different kinds of knowledge pertaining to oneself, either episodic or semantic. From the evidence of the amnesic patient KC, Tulving *et al.* (1988) proposed distinguishing between an episodic component (disturbed in KC), containing personal specific events situated in time and space, and a semantic component (preserved in KC), storing general knowledge of one's past. With the development of the theory of episodic memory, the essence of episodic memory has shifted away from its specificity to the phenomenal experience of remembering (Brewer, 1996; Baddeley, 2001; Tulving, 2001; Gardiner, 2001). More specifically, autonoetic consciousness, critically involved in episodic memory, is a feeling of re-experiencing or reliving the past and mentally travelling back in subjective time, while noetic consciousness, which

characterizes semantic memory, is the subject's ability to be aware of information about the world in the absence of any recollection (Tulving, 1985, 2001, 2002; Wheeler *et al.*, 1997). According to a constructive framework (Conway, 1996, 2001; Conway and Pleydell-Pearce, 2000), the recollection of autobiographical memories that ensures sense of remembering requires a complex retrieval process relying on the frontal lobe, which provides access to sensory/perceptual event-specific knowledge (i.e. images and feelings) via a personal semantic knowledge base (i.e. lifetime periods and generic events). Thus, given the multifaceted nature of autobiographical memory, it is necessary to have stringent methods of investigation, especially in order to demonstrate the existence of truly episodic autobiographical memories in patients (Moscovitch *et al.*, 1999), indicating not only their capacity to represent a specific event and locate it in time and space, but also their capacity to relive some specific feature of that event.

Above and beyond its clinical interest, because autobiographical memory is essential for personal identity and self-continuity, the investigation of autobiographical amnesia is critical to our understanding of neurocognitive models of long-term memory. According to the standard model of consolidation (McClelland *et al.*, 1995; Squire and Alvarez, 1995; Murre, 1996; Teng and Squire, 1999; Bayley *et al.*, 2003), the retrieval of recent declarative knowledge (episodic and semantic) mainly subserved by the neocortical regions is initially reliant on the MTL, but only for a time-limited period [from a few years for Graham and Hodges (1997) to 10 years for Reed and Squire (1998), and >10 years for Rempel-Clover *et al.* (1996)]. Such a model can explain impairment of recent memories in amnesic syndromes and early Alzheimer's disease (where the MTL is principally affected) and impairment of remote memory in semantic dementia and fv-FTD (where the neocortex is damaged but the MTL is relatively spared at the early stage). However, these theories do not distinguish between the episodic and semantic aspects of declarative memory, recently attested in several studies (Vargha-Khadem *et al.*, 1997; Gadian *et al.*, 2000; Guillery *et al.*, 2001). Moreover, they fail to fully explain evidence of global episodic retrograde amnesia (regardless of the time period) resulting from MTL damage (Nadel and Moscovitch, 1997; Fujii *et al.*, 2000; Cipolotti *et al.*, 2001; Rosenbaum *et al.*, 2001). Thus, an alternative model termed the 'multiple trace theory' (MTT), which takes the episodic and semantic nature of the stored information into account, concurs with the standard model of consolidation for semantic memory, but suggests that the MTL plays a permanent role in the storage and recovery of episodic memories (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1999b; Nadel *et al.*, 2000). This theory stresses that throughout a person's life, the MTL is involved in the recollection of the various parts of a particular episode, especially detailed contextual information such as place, emotional content and perceptual features. Otherwise, the frontal lobe would also play a role in temporal context memory (dating and temporal sequence).

Neurodegenerative pathologies are therefore particularly relevant in addressing the issue of remote episodic memory and may provide a situation in which the two competing theories of memory consolidation can be examined. According to the MTT, episodic retrograde amnesia should be dense and ungraded in Alzheimer's disease (where the MTL is affected), and relatively preserved, whatever the time interval, in semantic dementia (where the medial temporal and frontal lobes are preserved), providing that assessment is not too dependent on verbal skills (Moscovitch and Nadel, 1999a; Westmacott *et al.*, 2001). Recently, Westmacott *et al.* (2001) explored autobiographical memory in a patient with semantic dementia, using a procedure based on family photographs dating from infancy to the present day as cues in order to minimize the verbal contribution. They found that the patient had a well-preserved memory for autobiographical episodes, regardless of the time period, seemingly supporting the MTT. There was, however, no comparative data from control subjects, and the criteria for the episodic quality of the memories were not particularly strict. Lastly, in fv-FTD (where the frontal lobe is involved), the model predicts a reversed temporal gradient because the retrieval of remote memories requires more strategic processes than that of recent memories (Moscovitch and Nadel, 1999a). Nevertheless, the MTT might also predict a flat temporal gradient if the frontal lobe turns out to be crucial for the temporal context of memories regardless of their remoteness.

At present, given the low number of studies comparing autobiographical memory in neurodegenerative diseases, especially semantic dementia and fv-FTD, it is difficult to draw any firm conclusions about episodic retrograde amnesia, and it is therefore still premature to state which theory of memory consolidation is the soundest. The purpose of this study was to investigate episodic autobiographical memory over a time interval extending from the recent to the remote past in three groups of patients (Alzheimer's disease, semantic dementia, fv-FTD) relative to controls. The first aim was to test strictly episodic autobiographical memory and the issue of temporal gradient using an original method of assessment and checking procedures designed to be more valid and reliable than previous neuropsychological tests (Kapur, 1999; Nadel *et al.*, 2000). Secondly, we wanted to address the most up-to-date definition of episodic memory, which refers to a specific mode of subjective experience accompanying the retrieval of information—the auto-noetic component that is central to Tulving's concept of episodic memory (see above). In effect, although there has been a revival of interest in the study of consciousness and its relation to memory, only a handful of studies have investigated this issue in remote autobiographical memory (Dalla Barba *et al.*, 1997, 1999; Westmacott *et al.*, 2001; Hirano *et al.*, 2002). Thirdly, as one feature of episodic memory is the pulling together into a single episode of what, where and when something happened, we wanted to probe the different aspects of recollective experience, particularly the factual, spatial and temporal features of memories. In this way, we

could reliably test the two competing models (standard and multiple-trace) of long-term memory consolidation.

Material and methods

Subjects

Thirty-eight unmedicated patients with neurodegenerative disease and 18 normal controls were studied, all with at least 8 years of education. Every subject gave informed consent to the neuropsychological procedure, which was approved by the Ethical Committee of Caen University. All patients were selected on the basis of a neurological examination (CT scan or MRI) and a standard neuropsychological assessment. Patients with Alzheimer's disease were selected using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984). Patients with semantic dementia or fv-FTD were selected according to the consensus diagnostic criteria of Neary *et al.* (1998) and Hodges *et al.* (1999). For each group, the illness was at an early stage of dementia [mini-mental state examination (MMSE) ≥ 20 ; Folstein *et al.*, 1975] diagnosed within the last 2 years at the most. Patients with a history of alcoholism, significant head injury, neurological or psychiatric illness, or progressive non-fluent aphasia were excluded. Moreover, for the purposes of this study, we made sure that comprehension (i.e. anomia and impoverished general knowledge for concepts) and behavioural problems (i.e. signs of disinhibition, apathy, impulsiveness, loss of insight, social withdrawal or poor self-care)—critically involved in the semantic dementia and fv-FTD disease profiles—would not invalidate the performance of any of the patients on the autobiographical memory assessment. The behavioural changes were assessed using a modified French version of the Behavioural Assessment of Dysexecutive Syndrome (Wilson *et al.*, 1996). Clinical examinations and performances in the 'don't know schedule' of the Confabulatory Memory Battery of Dalla Barba (1993) did not reveal any major signs of confabulation in the fv-FTD group.

Thirteen Alzheimer's disease patients (age: mean \pm SD = 73.1 ± 5.5 years; range 61–81 years), 10 semantic dementia patients (age: 69.9 ± 4.2 years; range 63–76 years) and 15 fv-FTD patients (age: 67.8 ± 9.4 years; range 52–78 years) were compared with 18 control subjects (age: 69.4 ± 2.9 years; range 65–75 years), paired according to their age and level of education. Control subjects were recruited from retirement homes, and were in good mental and physical health and free from any medication known to affect the CNS. There was no statistical difference by ANOVA (analysis of variance) for age and education level between the different groups of patients. Duration of the pathology did not significantly differ between the three groups of patients, though the semantic dementia and fv-FTD groups showed less severe dementia as

measured by the MMSE score (26.4 ± 1.5 ; 25.6 ± 1.9 , respectively) than the Alzheimer's disease group (22.3 ± 2.1).

General cognitive assessment

For all three groups of patients, in addition to MMSE, a general cognitive examination was used to explore semantic memory by means of category fluency (names of animals) and letter fluency tasks (words beginning with p) (Cardebat *et al.*, 1990) and a semantic knowledge task (Giffard *et al.*, 2001). The latter, which is derived from Martin *et al.* (1986) and Desgranges *et al.* (1996, 1998a), involves three components (picture naming, categorical knowledge and attribute knowledge of concepts) of 30 concepts belonging to four categories (animals, plants, objects and body parts). First, subjects have to name 30 drawings corresponding to the 30 concepts or recognize the name if they cannot do so. They then have to answer 'yes' or 'no' to a series of questions about the concepts: superordinate category ('does it occur naturally or is it manmade?'); category membership ('is it an animal, plant, object or body part?'); subcategory ('is it a domestic or a wild animal?'); and specific attribute, either functional ('is it edible?') or perceptual ('does it have a mane?').

A verbal episodic memory test (Eustache *et al.*, 2001), derived from Grober and Buschke's procedure (1987), was conducted in order to examine the encoding of information in episodic memory using words whose semantic integrity had previously been checked in the semantic knowledge task. The subjects learn 15 items presented three at a time on a card, pointing out and naming each item when its category cue is presented verbally. They are then asked for an immediate verbal cued recall. If a subject fails to recall an item, the card is shown again. This encoding phase is followed by three recall tests—first a free recall and, if necessary, a categorical cued recall test, then a recognition memory test. Each trial is preceded by 20 seconds' interference when patients are asked to count backwards. After 20 min, delayed free and cued recalls are tested.

Working memory was evaluated by a digit span test (forward and backward; Wechsler, 1991), executive functions by the Wisconsin Card Sorting Test (Nelson, 1976) and the Stroop test (Stroop, 1935). Visuo-spatial abilities were measured by copying a complex figure (Rey, 1960). Finally, language was assessed by means of a picture naming task (DO 80: Deloche and Hannequin, 1997), where the subject has to name 80 black and white line drawings of familiar objects and, in the case of the semantic dementia patients, the Token test (De Renzi and Faglioni, 1975).

The neuropsychological examination (Table 1) revealed distinct profiles consistent with previous studies (Elfgrén *et al.*, 1993; Hodges *et al.*, 1999). The Alzheimer's disease group showed the greatest disturbance of episodic anterograde memory and visuo-spatial abilities, as well as some working memory and executive difficulties (backward digit span and Stroop test). The semantic dementia group displayed isolated semantic memory difficulties with anomia and an

Table 1 Neuropsychological data (mean \pm SD) for all three groups of patients. Differential effects between the three groups of patients are reported (ANOVA)

	Tests	Norms [†]	Alzheimer's disease	Semantic dementia	fv-FTD	Group effect
Semantic memory	Category fluency	27.1 (8.5)	11.3 (4.9)	16.8 (7.3)	16.3 (4.9)	ns
	Letter fluency	19.3 (7.0)	7.5 (9.1)	13.1 (5.6)	12.7 (7.0)	ns
	Semantic Knowledge Task (SKT): total score (/236)	232 (2.0)	228 (7.6)	199.5 (34.9)	222 (12.9)	*(1)
	SKT: naming (/60)	59.3 (0.7)	57.3 (3.0)	49 (10.1)	58 (3.3)	*(1)
	SKT: categorical knowledge (/86)	84.7 (1.0)	83.1 (3.8)	76.7 (13.6)	80.2 (10.1)	ns
Episodic memory	SKT: attribute knowledge (/90)	87.9 (1.9)	87.5 (2.3)	73.7 (12.8)	83.8 (5.0)	*(1)
	Immediate recall (/15)	15.0 (0)	11.7 (3.5)	14.6 (0.9)	13.8 (1.9)	ns
	Total recall (/45)	43.8 (1.2)	24.1 (9.6)	36.4 (7.0)	35.1 (8.7)	** (2)
	Delayed recall (/15)	14.9 (0.3)	9.1 (5.4)	11.8 (3.9)	11.6 (3.6)	ns
Working memory	Recognition (/45)	44.5 (0.8)	38.8 (5.9)	42 (2.6)	39.8 (7.7)	ns
	Forward digit span	7.2 (1.9)	5.2 (1.5)	6.6 (1.7)	5.2 (1.1)	ns
Executive functions	Backward digit span	5.9 (2)	2.7 (0.9)	5.1 (1.2)	3.5 (1.3)	** (3)
	Wisconsin Card Sorting Test (category number)	6 (1.1)	1.7 (0.8)	4.7 (2.5)	NR	*(4)
	Wisconsin Card Sorting Test (perseveration)	1.2 (2)	10.3 (7.2)	4.3 (3.5)	NR	**** (5)
Visuo-spatial abilities	Stroop (Interference)	0 (10)	3.2 (4.1)	14.4 (14.3)	-5.4 (11.3)	** (6)
	Rey complex figure copying (/36)	33.9 (2.4)	17.8 (15.9)	33.6 (1.1)	31.1 (3.0)	** (2)
Language	Picture naming task (DO 80)	69 [‡]	69.3 (10.8)	55.6 (11.2)	76.0 (5.7)	*** (7)
	Token test (/36)	29 [‡]	NT	33.0 (2.1)	NT	-

[†]Normative data are provided for information only; [‡]Pathological cut-off; NT = not tested; NR = non realizable for most of the patients; ns = non significant. The results of a one-way ANOVA (group) and *post hoc* analysis (PLSD Fisher) are shown according to performances on each test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.10$; ⁽¹⁾Semantic dementia < Alzheimer's disease = fv-FTD; ⁽²⁾Alzheimer's disease < semantic dementia = fv-FTD; ⁽³⁾Alzheimer's disease = fv-FTD < semantic dementia; ⁽⁴⁾Alzheimer's disease < semantic dementia; ⁽⁵⁾Semantic dementia < Alzheimer's disease; ⁽⁶⁾fv-FTD = Alzheimer's disease < semantic dementia; ⁽⁷⁾Semantic dementia < Alzheimer's disease < fv-FTD.

impoverished general knowledge on concepts (the naming task and semantic knowledge task), especially for attribute categorization compared with the other patient groups. As for the fv-FTD group, the tests revealed executive dysfunctioning (Stroop, Wisconsin) and working memory difficulties (backward digit span).

Autobiographical memory task

This task consists of a semi-structured questionnaire (Piolino *et al.*, 2003) based on those used by Kopelman *et al.* (1989), Borroni *et al.* (1989) and Piolino *et al.* (2002), which assesses the ability to recall detailed specific events situated in time and space from five time periods covering the entire lifespan: (i) 0–17 years old; (ii) 18–30 years old (iii) >30 years old except for the last 5 years; (iv) last 5 years except for the last 12 months; and (v) last 12 months. There is no time limit, but the test generally lasts 2 h. Participants are first asked to describe personal events in as much detail as they can. They then have to give a subjective report of their state of consciousness during retrieval from autobiographical memory. According to Tulving's theory (1985), remembering and knowing are two different states of consciousness, which reflect auto-noetic and noetic consciousness respectively, i.e. episodic and semantic memory. The subjective phenomenal experience can be assessed via the remember/know (R/K) paradigm (Tulving, 1985; Gardiner, 1988), which requires subjects to give either a 'remember' (R) response if retrieval

is accompanied by the recollection of specific experiences present at encoding, or a 'know' (K) response if retrieval is achieved without access to information from the initial learning context. A 1 h re-test was carried out 15 ± 2 days after the task in order to check each memory. This consisted of a cued recall task where subjects had to recall in random order the content and the time and spatial location of each recollected event. Where possible, a family member also checked each memory.

The questionnaire

Each time period examined, with the exception of the most recent one, was assessed on four topics (a meeting or an event linked to a person, a school and then a professional event, a trip or journey, a familial event), with instructions such as 'give details of a particular event which took place during your family life'. For the most recent period, eight questions allowed a chronological study of the previous 12 months: last summer; Christmas or New Year's Day; last week; last weekend; 2 days ago; yesterday; and today. Again, subjects were given instructions such as 'give details of a particular event which occurred last week'. If a participant could not spontaneously recollect a specific event, cues were provided (for example, 'on a day with a teacher or friend', 'in primary or secondary school', 'in the school playground' or 'during an exam'), while he or she was encouraged to be specific if the memory was generic (e.g. do you remember a particular

day?). After three cueing and/or encouragement attempts, the tester switched to another topic.

Scoring. Each recalled event was scored on a four-point episodic scale based on that used by Baddeley and Wilson (1986). This scale took into account the specificity of the content (single or repeated event), the time and spatial location, and the presence of details (perceptions, thoughts or feelings). A specific event with details and situated in time and space was given a score of four points. A specific event without any detail but situated in time and space scored three points. A repeated or extended event scored two points or one point, depending on whether or not it was situated in time and space. Absence of memory or general information about the topic, scored zero. The critical factor which allowed us to differentiate between a specific event (scored three) and a specific, detailed event (scored four) was the failure, despite much encouragement, to add details concerning the source of acquisition. Recollections scoring two or one referred rather to personal semantic memory. Two different total scores were recorded per time period examined. The overall autobiographical memory score (AM: maximum $4 \times 4 = 16$) corresponded to the classic episodic memory score used in the Autobiographical Memory Interview (Kopelman *et al.*, 1989), which takes into account all types of recall, both specific and generic. For the purposes of our investigation, it was crucial to study specific memories separately. We therefore used a very stringent criterion in the form of a strictly episodic memory score (EM: maximum $4 \times 4 = 16$), for memories which were specific in time and space and richly detailed (scored four on the four-point episodic scale). We paid no attention to specific non-detailed memories considering that it was the details, and the details alone, which made it possible to reliably assess whether a memory was truly episodic (Moscovitch *et al.*, 1999).

The R/K paradigm

Following the recall of each event, the subjects had to indicate whether or not they could consciously recollect its prior occurrence by making separate R/K judgments for the content, place and date of the event (what, where and when, respectively). They could also indicate if they had simply guessed the recalled event (Mäntylä, 1993). It is important to note that the judgment categories (Tulving, 1985; Gardiner, 1988; Conway *et al.*, 1997) were explained very carefully to the patients until each concept used in this test was thoroughly understood. First of all, the subjects were instructed to select one of these categories (i.e. remember, know or guess) with reference to the factual content (what) of the recalled event, according to whether they:

(i) Remembered the specific episode with its encoding context. In this case, they might virtually relive some of the details surrounding the recalled event, such as feelings or images.

(ii) Just knew this episode had happened to them, but could not recall any specific event and could not virtually relive details related to it.

(iii) Just guessed that they might have experienced this episode, but neither remembered nor knew it.

The subjects were then instructed to select the appropriate categories for the place and date of the event.

Lastly, a procedure was performed to check whether the subjects could justify each of their 'R' judgments, proving that they had effectively relived some aspects of the original event. Accordingly, for each R response provided for the three kinds of information (what, where and when), the subjects had to add contextual details from the original event, if they had not already provided them spontaneously: phenomenal details such as their thoughts, feelings or perceptions for the content (what), spatial details and location for the place (where) and time of day or temporal sequence for the date (when). The 'justified R' procedure was rather similar to the approach adopted by Moscovitch *et al.* (1999), who classified details retrieved for each cue word provided into various categories such as perceptual (visual-auditory), emotional, spatial and temporal involvement.

Scoring. As the aim of our study was to investigate episodic memory in patients, we restricted our analyses to the Remember responses, awarding: (i) a remember score (R: maximum $3 \times 4 = 12$) for the total number of R responses provided, irrespective of the kind of information (what, where, when); and (ii) a justified remember score (justified R: maximum $3 \times 4 = 12$) for the number of R responses effectively associated with the recollection of a single event with contextual details (thoughts, feelings or perceptions for content, location for place, and time of day or temporal sequence for date). In order to investigate the impact of the kind of information on performances, these two episodic indicators were studied separately, according to the three types of information (what, where and when). For example, for each time period, the 'where remember score' corresponded to the number of R responses given for the spatial features of the recalled events (maximum $1 \times 4 = 4$).

It is worth mentioning that the overall autobiographical memory score, strictly episodic memory score and justified remember scores were all established on the basis of the information supplied in the test and corroborated in the retest and by a family member. Each score for the last 12-month period, which concerned eight items instead of four topics, was halved. Two independent experts rated each memory until a consensus was reached.

Data analyses

Statistical analyses of the data recorded on the autobiographical memory task, expressed in terms of a total score per period, were processed using a repeated measure ANOVA, followed by *post hoc* tests [protected least significant differences (PLSD) Fisher] to examine the influence of the factors of group (controls, Alzheimer's disease, semantic

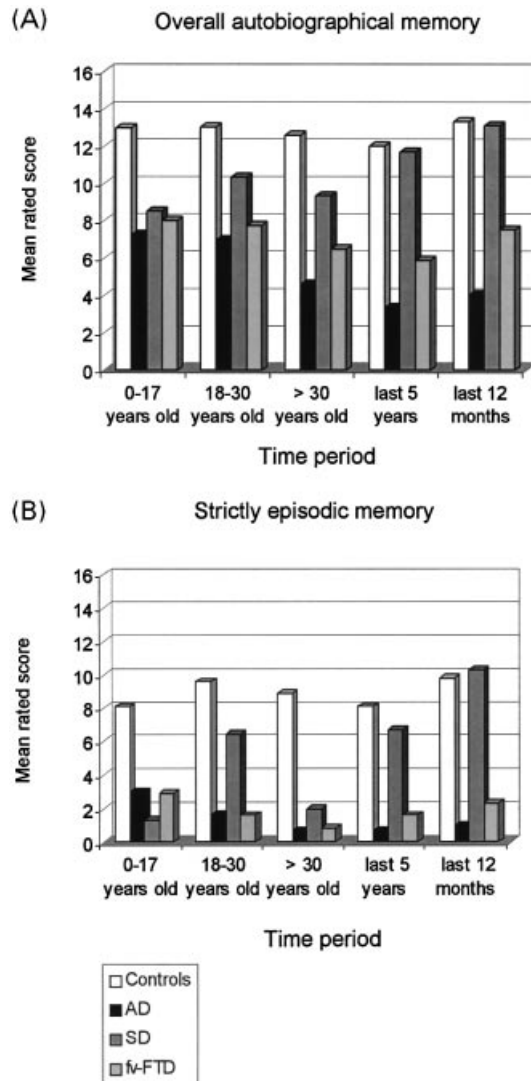


Fig. 1 Patients' results on the episodic autobiographical memory task compared with those of the control subjects for each time period: (A) overall autobiographical memory score (AM) and (B) strictly episodic memory score (EM). AD = Alzheimer's disease; SD = semantic dementia; fv-FTD = frontal variant of frontotemporal dementia. Controls ($n = 18$); AD ($n = 13$); SD ($n = 10$); and fv-FTD ($n = 15$).

dementia, fv-FTD) as between factor, time period (0–17 years old, 18–30 years old, >30 years old except for the last 5 years, last 5 years except for last 12 months, last 12 months) and type of information (what, where, when) as within factors.

Results

Autobiographical memory retrieval

Fig. 1 shows the results for the AM and the EM. An ANOVA (group, period) performed for these two scores showed a significant main effect of group [$F(3,52) = 39.28$ and 30.30 , $P < 0.0001$, respectively] and time period [$F(4,208) = 7.85$, $P < 0.0001$ and 4.77 , $P < 0.01$]. *Post hoc* pair-wise

comparisons showed that the total performances of patients for both scores were poorer than those of the control subjects, with semantic dementia being less impaired than Alzheimer's disease and fv-FTD (performances on controls > semantic dementia > Alzheimer's disease = fv-FTD). The group by time period interaction was also significant [$F(12,208) = 3.66$ and 3.38 , $P < 0.0001$] and indicated that the time period effect differed from one group to another.

A series of one-way ANOVAs (period) carried out for each group showed differential results:

(i) For the control group, the analysis showed a significant period effect for AM score, but no effect for the EM score [$F(4,68) = 3.29$, $P < 0.05$; $F(4, 68) = 1.76$, $P = 0.13$, respectively]. The AM score for the 5-year period was significantly lower than the score for all the other periods.

(ii) For the Alzheimer's disease group, the analysis showed a significant period effect for the AM score, but no effect for the EM score [$F(4,48) = 3.74$, $P < 0.05$; $F(4,48) = 1.31$, $P = 0.28$]. The AM score for the two earliest periods was higher than the one for the other periods.

(iii) For the semantic dementia group, the analysis showed a significant period effect for both scores [$F(4,36) = 6.64$, $P < 0.01$; $F(4,36) = 10.10$, $P < .0001$]: the most recent period scored higher than the other periods ($P < 0.0001$), while the 18–30 years period (comparable to the 5-year period) scored better than the two adjacent periods, indicating a reminiscence bump.

(iv) For the fv-FTD group, the analysis showed a significant period effect for the AM score [$F(4,56) = 5.27$, $P < 0.01$], but no effect for the EM score [$F(4,56) = 1.56$, $P = 0.19$]. The last 5-year period scored lower than the other periods (U-shape similar to that of the controls).

In summary, for the AM scores, patients with Alzheimer's disease showed a temporal gradient, with scores being numerically higher for the most remote periods, whereas patients with semantic dementia demonstrated the reversed gradient, with the most recent period being better preserved than the others. The fv-FTD group presented no clear time gradient. The EM scores were particularly low for all the patient groups, compared with the controls, with the exception of the most recent 12-month period for the patients with semantic dementia.

State of consciousness accompanying autobiographical retrieval

Fig. 2 illustrates the results obtained for R and justified R scores in the form of curves indicating mean performance according to group, type of information and time period. For both scores, a three-way ANOVA (group, period, information) (repeated measures ANOVA with two within factors, information and period) was carried out to compare performances according to the type of information (what, where or when), group and time period.

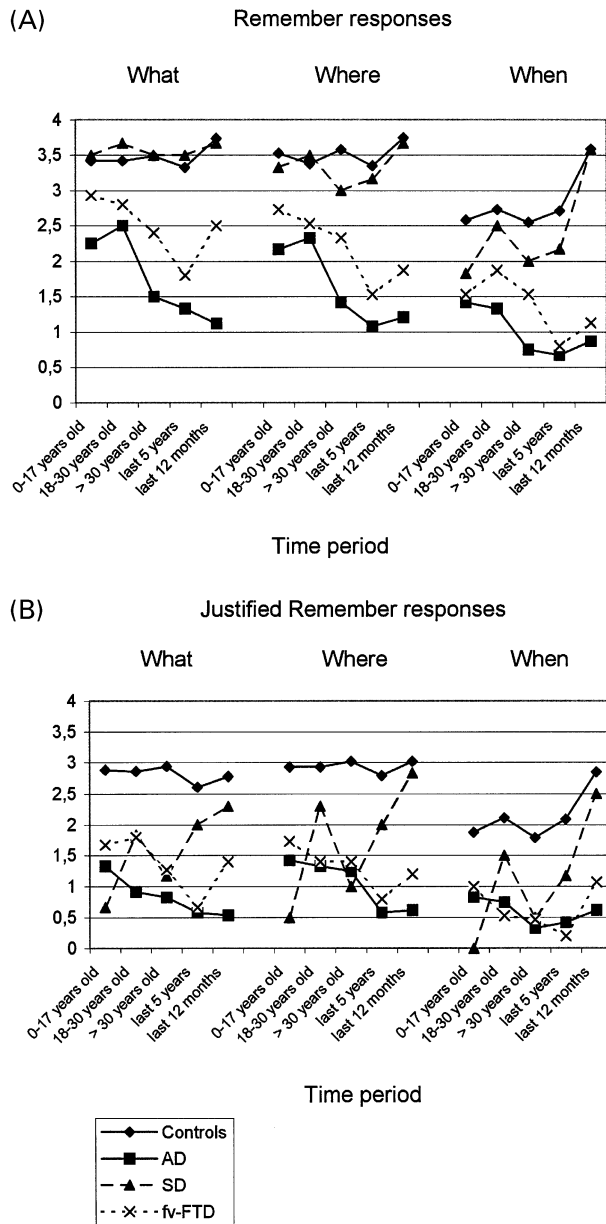


Fig. 2 Means of (A) remember responses (R) and (B) justified remember responses (justified R) as a function of group and type of information for each of the five time periods. AD = Alzheimer's disease; SD = semantic dementia; fv-FTD = frontal variant of frontotemporal dementia.

The ANOVA performed for the two scores (R and justified R) revealed simple effects of group [$F(3,52) = 37.5$ and 34.35 , $P < 0.0001$; performances on controls = semantic dementia > fv-FTD > Alzheimer's disease and controls > semantic dementia = fv-FTD = Alzheimer's disease respectively], period [$F(4,208) = 7.96$ and 5.45 , $P < 0.0001$; performances on last 5 years < other time periods], and information [$F(2,104) = 70.58$ and 16.81 , $P < 0.0001$; performances on what = where > when]. Both the information by period [$F(8,416) = 7.85$ and 3.86 , $P < 0.0001$, see Fig. 2] and the group by period interactions

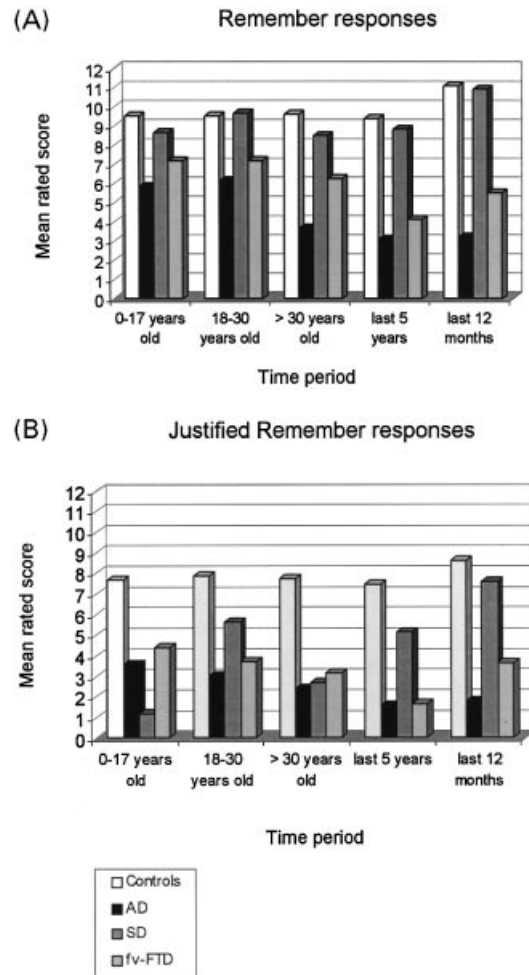


Fig. 3 Patients' auto-noetic consciousness results for each time period: (A) number of total remember responses (R) and (B) total justified remember responses (justified R). AD = Alzheimer's disease; SD = semantic dementia; fv-FTD = frontal variant of frontotemporal dementia.

[$F(12,208) = 3.60$ and 4.55 , $P < 0.0001$, see Fig. 3] were significant. Firstly, for the R scores and justified R scores, *post hoc* analyses indicated that the best performances on the 'what' and 'where' scores were for the two earliest periods, whereas the best performances on the 'when' scores were for the most recent period. Secondly, the period effect varied across the groups: control group (for both scores, performances on last 12 months > other periods), Alzheimer's disease (for R scores, performances on 0-17 = 18-30 > other periods and, for justified R scores, no difference across periods), semantic dementia (for R scores, no difference across periods and, for justified R scores, performances on last 12 months > last 5 years = 18-30 > other periods) and fv-FTD (for both scores, performances on last 5 years < other periods). Moreover, the group by information interaction (see Fig. 4) was significant for the R scores, but not for the justified R scores [$F(6,104) = 2.27$, $P < 0.01$; $F(6,104) = 0.65$, $P = 0.69$, respectively]. *Post hoc* analyses showed significant main

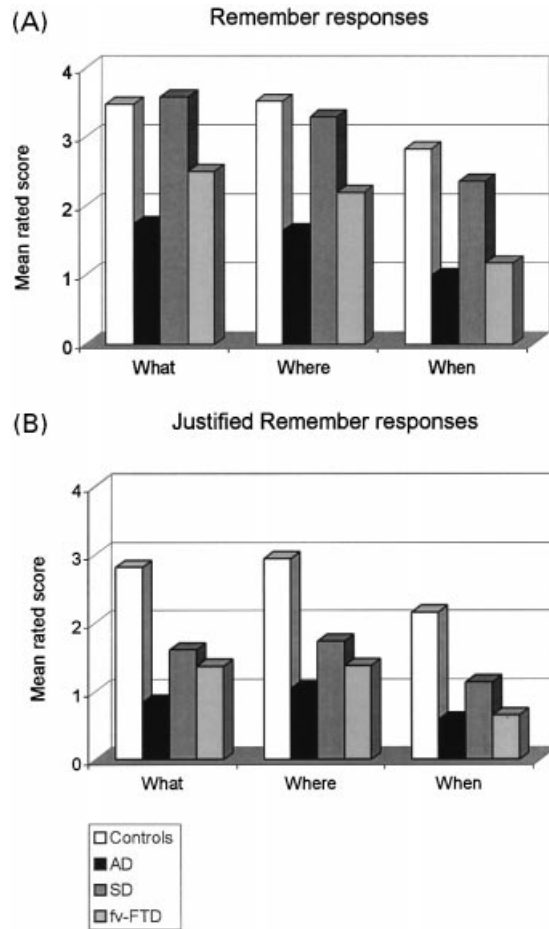


Fig. 4 Patients' autoecognitive consciousness: number of remembered responses (A) and justified remembered responses (B), according to the type of information (what, where or when).

AD = Alzheimer's disease; SD = semantic dementia; fv-FTD = frontal variant of frontotemporal dementia.

effects of group which varied across the type of information: what and where R scores (performances on controls = semantic dementia > fv-FTD > Alzheimer's disease) and when R scores (performances on controls = semantic dementia > fv-FTD = Alzheimer's disease). The triple interaction was not significant [$F(24,416)$, $P > 0.10$].

In summary, with regard to the state of consciousness assessment as a function of period and type of information tested (what, where and when), our results mainly indicated deficits of R responses for the Alzheimer's disease and fv-FTD groups, but not for the semantic dementia group. However, the justified R responses were always impaired compared with the controls, regardless of the patient group and type of information, though less so for the semantic dementia patients.

Discussion

Based on a stringent criterion, this study was designed to investigate the deficit of episodic remote memory and the presence of temporally graded memory loss in different

Table 2 Triple dissociation in dementias: synopsis of results from the autobiographical memory assessment

	Alzheimer's disease	Semantic dementia	fv-FTD
Recent memory (last 12-month period)			
AM	—	+	—
EM	—	+	—
R	—	+	—
Justified R	—	+	—
R: what/where/when	—/—/—	+/+/+	-/-/-
Remote memory			
AM	— (TG)	— (rTG)	— (FG*)
EM	— (FG)	— (RE, RBE)	— (FG)
R	— (TG)	— (FG)	— (FG*)
Justified R	— (FG)	— (RE, RBE)	— (FG*)
R: what/where/when	—/—/—	+/+/+	-/-/-

The performances are shown in the table according to the results of the ANOVAs (see Results) relative to the controls:

+ = preserved; — = disturbed; — = severely disturbed.

AM = overall biographical memory score; EM = strictly episodic memory score; R = remember responses; RE = recency effect (last 5 year period relatively preserved); RBE = reminiscence bump effect (18–30 years period relatively preserved); TG = Ribot's temporal gradient; rTG = reversed Ribot's temporal gradient; FG = flat gradient; FG* = no clear gradient (U-shape; performances for the last 5 years poorer than for all the other periods).

neurodegenerative diseases. The experiment highlighted contrasting profiles of autobiographical retrograde amnesia, according to the neurodegenerative pathology (see Table 2 for synopsis). We begin by discussing the issue of temporal gradient in autobiographical amnesia in relation to type of memory. We then examine the results from the state of consciousness study with respect to the difference between phenomenological, spatial or temporal features of memories on the one hand, and between subjective judgment and checking procedure on the other. These results provide a firm basis on which to discuss the standard and MTT models of long-term memory consolidation in the light of the conceptions of autobiographical memory retrieval.

Autobiographical memory retrieval in dementia

Using an overall autobiographical score (i.e. the classic measure, AM score) which took into account all types of recall (both specific and generic), the results revealed that compared with the controls, the three patient groups exhibited a deficit of autobiographical memory with distinct temporal profiles consistent with previous studies: a gentle Ribot's temporal gradient in Alzheimer's disease (Kopelman, 1989, 1992; Graham and Hodges, 1997; Thomas-Antérion *et al.*, 2000), a reversed temporal gradient in semantic dementia (Snowden *et al.*, 1996; Graham and Hodges, 1997; Piolino *et al.*, 2003) and an absence of any clear temporal gradient in fv-FTD (Thomas-Antérion *et al.*, 2000; Nestor *et al.*, 2002). Like the control group, the fv-FTD patients, however, showed

a U-shaped curve; the memories from the remote and recent time-periods being comparable and better than those from the intermediate period (last 5 years). The Alzheimer's disease and fv-FTD patients, though not the semantic dementia patients, showed impairment for all the time periods.

Using a strict assessment criterion (i.e. specificity in time and space and richness of details, EM score) to investigate the integrity of episodic autobiographical memory across the entire lifespan, our findings revealed notable differences in performance levels compared with the overall autobiographical score. Moreover, we documented an ungraded autobiographical amnesia for Alzheimer's disease and fv-FTD patients, but a reversed temporal gradient for semantic dementia patients. Although all three patient groups definitely produced fewer memories than the controls, few specific memories were produced in accordance with the final experiment in the study carried out by Nestor *et al.* (2002) which also compared the performances of three patient groups (Alzheimer's disease, semantic dementia, fv-FTD) on memories that were specific in time and space, excluding generic ones, using a Crovitz paradigm (Crovitz and Schiffman, 1974). These authors recorded a higher number of specific memories than we did in our study, perhaps because they did not take the richness of detail into account. The patients with Alzheimer's disease tended to deteriorate less towards the most remote period although, like Nestor *et al.* (2002), we did not note any significant temporal gradient. The comparison between the profiles of overall autobiographical memories and strictly episodic ones (i.e. AM and EM) highlighted their difficulty in retrieving truly episodic memories compared with more generic autobiographical ones. These data support the view that preserved remote memories in Alzheimer's disease have a predominantly semantic character (Cermak, 1984; Butters and Cermak, 1986; Warrington and Mc Carthy, 1988), especially for the oldest memories spanning the first 17 years of life. For the fv-FTD group, as was the case with the Alzheimer's disease patients, strictly episodic memories were very scarce regardless of the time period. The latter produced poorly detailed generic events—a finding which is consistent with previous studies of patients with non-progressive frontal injury revealing a deficit of access to specific autobiographical memories (Baddeley and Wilson, 1986; Della Sala *et al.*, 1992, 1993; Kopelman *et al.*, 1999; for reviews, see Conway and Fthenaki, 2000; Kopelman and Kapur, 2001).

The performance of patients with semantic dementia showed a clear recency effect for the most recent 12-month period, with the earliest time period (0–17 years old) and the late adulthood period (>30 years old) being the most affected. The presence of a step-like effect accords with previous single-case studies (patient AM: Graham and Hodges, 1997; patient JH: Nestor *et al.*, 2002) using the Galton paradigm (Crovitz and Schiffman, 1974) and a fine-grained scoring chart, which demonstrated that the majority of specific memories came from the last 5 years. Our findings also revealed the survival of specific detailed memories from both

the most recent 5-year period and the remote past, where the young adulthood period, from 18 to 30 years old, was relatively well-preserved compared with adjacent periods. Interestingly, the average performance of this group of 10 semantic dementia patients confirmed a previous investigation of a single semantic dementia patient (Piolino *et al.*, 2003). These memories corresponded to the reminiscence bump observed in aged subjects, concerning the surge of 'strictly' episodic memory involving vivid and important memories, which are more easily accessible (Rubin *et al.*, 1986; Fitzgerald, 1996; Conway and Rubin, 1993; Rubin and Schulkind, 1997; Piolino *et al.*, 2002). As suggested by Moscovitch and Nadel (1999a), the episodic profile of the semantic dementia patients, which was characterized by a recency effect and a reminiscence bump, resembles that which is typically observed in controls when the test is made relatively difficult in order to avoid a ceiling effect (Piolino *et al.*, 2002). According to some authors (Moscovitch and Nadel, 1999a; Nadel *et al.*, 2000; Westmacott *et al.*, 2001), evidence of such remote memories would be sufficient to prove that remote episodic memory is relatively preserved in semantic dementia, though limited by a deficit of access and restricted verbal skills. Nevertheless, this result concerned only four of the 10 patients with semantic dementia. This heterogeneity among semantic dementia patients has been highlighted by Snowden *et al.* (1996) and documented in several studies which have shown a relative preservation of remote autobiographical memories in case studies (Kitchener and Hodges, 1999; Moss *et al.*, 2000; Nestor *et al.*, 2002; see experiment 1b, single case DM, first assessment; Piolino *et al.*, 2003). It is notable that the performances observed in our study differed according to the type of measurement used (EM score, i.e. specific and detailed, or AM score, i.e. both specific and generic). As such, they confirm the usefulness of taking into account the presence of details associated with specific memories, in order to reliably identify residual episodic memories (Moscovitch *et al.*, 1999).

State of consciousness accompanying memories in dementia

With regard to the R/K procedure, the Alzheimer's disease and fv-FTD patients, but not the semantic dementia patients, reported significantly fewer R responses than the controls. Moreover, the Alzheimer's disease patients gave fewer responses than the fv-FTD patients for the phenomenological and spatial features of personal events, although they gave as many as the fv-FTD patients for the temporal features. As regards the profile of the Alzheimer's disease patients, our data highlighted the critical involvement of the MTL in spatial memory (Nadel *et al.*, 2000; Rosenbaum *et al.*, 2001). As far as the fv-FTD patients are concerned, our data showed that source amnesia for temporal information concerns both remote and recent memory, thereby corroborating previous reports on retrograde amnesia (Thomas-Antérion *et al.*, 2000)

and anterograde amnesia (Simons *et al.*, 2002). This abnormality in temporal context memory has also been found in patients with non-progressive frontal lobe lesions (Kopelman *et al.*, 1997). Our findings showed that the Alzheimer's disease and fv-FTD patients subjectively 'felt' that they were mentally reliving the source of their memories to a significantly lesser degree than the controls and the semantic dementia patients did. Thus, like previous studies on states of consciousness in amnesic patients (Knowlton and Squire, 1995; Hirano *et al.*, 2002) or Alzheimer's disease (Dalla Barba *et al.*, 1997), it implies that a disruption of auto-noetic consciousness contributes to poor performances of Alzheimer's disease and fv-FTD patients in autobiographical event memory. Indeed, a number of converging lines of evidence have suggested that the sense of remembering depends on both the frontal lobe (Wheeler *et al.*, 1997; Levine *et al.*, 1998) and the MTL (Knowlton, 1998; Tulving and Markowitsch, 1998). Recently, Hirano *et al.* (2002), regarding the fact that their patient with amnesic syndrome (single case YK) showed rare autobiographical remembering accompanied by subjective experience (R responses), concluded that his remote autobiographical memory was not based on episodic memory but rather on semantic memory. In contrast, the findings from the semantic dementia patients may suggest a preservation of auto-noetic consciousness at the early stage of the disease, and therefore a relative preservation of episodic memory *per se*. The R/K paradigm may reveal memories that would otherwise be underestimated. This interpretation is in accordance with the recent proposal by Westmacott *et al.* (2001) who, in a patient with semantic dementia (single case EL), observed a preservation of the sense of remembering signalled by phrases such as 'I remember...', triggered by personal photographs covering his entire life span, although this evidence was not based on the R/K paradigm.

However, using our procedure to check subjective reports (justified R responses), we showed that the semantic dementia patients, albeit to a lesser degree than the Alzheimer's disease and fv-FTD patients, were unable to justify all their R judgments, failing to provide as many episodic details (i.e. feelings, thoughts or images, location or time) about a specific occurrence as the control subjects. Thus, the feeling of reliving the past reported by the semantic dementia group, with the exception of the most recent 12-month period (and, to a lesser degree, the last 5 years and the young adulthood periods), would appear to have been more subjective than was objectively demonstrated by the narrative report of their memories. It is, however, worth noting that this checking procedure is much more dependent on verbal skills than the classic R/K paradigm.

Mechanisms of autobiographical amnesia in dementia

The remaining question is how memory consolidation theories can explain the present results. Our findings may

have some reliable implications, as they are based on an experimental investigation which explores the entire lifespan, using a strict episodic criterion (strictly episodic score, R/K procedure) and a triple checking procedure (justified R procedure, retest, verification with a family member where possible).

The 'standard model' of consolidation suggests that, after a time-limited period, the retrieval of information stored in neocortical areas takes place independently of the MTL. This model may provide a suitable explanation for some of our results (see Table 2). The differential patterns of autobiographical amnesia, notably the opposite gradients observed for the overall autobiographical memory score in Alzheimer's disease (Ribot's gradient) and semantic dementia (reversed Ribot's gradient), support for the time-limited involvement of the MTL in the storage and retrieval of information proposed by several authors (Snowden *et al.*, 1996; Graham and Hodges, 1997; Hodges and Graham, 1998; Graham, 1999; Graham *et al.*, 1999). However, in the Alzheimer's disease group, the presence of an extensive temporal gradient stretching back over 40 years (AM) or the entire lifespan (for EM) may imply that consolidation continues for far longer than just a few years. In the semantic dementia patients, the preservation of recent memories relative to more distant strictly episodic ones (i.e. EM and justified R) is in keeping with the idea that the temporal neocortex is a crucial site for the storage of knowledge and past autobiographical experience (Graham and Hodges, 1997; Hodges and Graham, 1998; Murre *et al.*, 2001). Since the anterior temporal lobe plays a well-known role in semantic memory, this may imply that remote autobiographical memory acquires a semantic nature, whereas recent memories remain episodic (Cermak, 1984). This would explain why remote memories are lost in semantic dementia and better preserved in Alzheimer's disease. This interpretation has been proposed in classic amnesic syndrome, in order to explain Ribot's gradient (Butters and Cermak, 1986; Schmidtke and Vollmer, 1997). Nonetheless, Graham and Hodges (1997) point out that the very short-term preservation of autobiographical memory (just a few years) cannot really be explained by a semanticization process unless this process occurs very rapidly. Moreover, our results in the semantic dementia group (i.e. reminiscence bump effect and R), argue in favour of the existence (albeit rare) of remote episodic memories. In order to explain the profile of these performances in semantic dementia patients, the standard model must emphasize that episodic memory is sustained by the MTL for the recent past and by the neocortex for the remote past (Bayley *et al.*, 2003). The deficit without any clear time gradient in fv-FTD may also be compatible with the standard model of memory consolidation, though it does suggest that the MTL alone cannot ensure the normal retrieval of recent autobiographical memories in the case of frontal damage, as opposed to temporal neocortex damage. Finally, some of our results are problematic for the standard model, especially the flat gradient in Alzheimer's disease (i.e. EM). In particular, this

model fails to elucidate the difference in profiles according to the type of memories (semantic or strictly episodic) being studied (Piolino *et al.*, 2003).

The ‘multiple trace theory’ can explain the flat gradients (i.e. EM) observed in the Alzheimer’s disease and fv-FTD patients by proposing that episodic recollection always depends on the MTL, regardless of the time interval, as well as on the frontal lobe for temporal indexing in recollection (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1999b; Nadel *et al.*, 2000; Westmacott *et al.*, 2001). In particular, the MTT may explain the difference in profiles in Alzheimer’s disease according to the memory score investigated in our study (AM or EM) as this model assumes that personal semantic memory, unlike episodic memory, becomes independent of the MTL over time, as proposed by the standard model. Therefore, the profiles of performances for the overall autobiographical score (which concerned semanticized memories far more than strictly episodic ones) are in keeping with a limited role of the MTL (see above), whereas the profiles of performances for the strictly episodic score and auto-noetic consciousness may be compatible with a permanent role of the MTL.

As far as the semantic dementia patients are concerned, the well-preserved subjective sense of remembering (R), critically involved in episodic recollection (Tulving, 2001, 2002), fits in with the MTT’s prediction about this disease (Moscovitch and Nadel, 1999a). The issue of the discrepancy between the R and justified R judgements in semantic dementia becomes crucially important when we start trying to decide which model of consolidation is best supported by our data. If we consider that the preservation of R responses in semantic dementia supports the idea of a relative preservation of episodic memory per se, why were the patients not able to justify their responses by recollecting contextual details? The MTT has put forward three different pertinent explanations for the presence of a reversed temporal gradient in semantic dementia, which might explain the profiles (i.e. EM and justified R) of our semantic dementia patients. First, Nadel and Moscovitch (1997) suggest that this kind of profile may depend on a deficit of strategic retrieval caused by additional frontal pathology, as the frontal lobe is often involved in this disease (Neary *et al.*, 1998; Edwards-Lee *et al.*, 1997; Graham *et al.*, 1999; Hodges *et al.*, 1999; Mummery *et al.*, 1999, 2000). However, when Nestor *et al.* (2002, see experiment 2), looked at whether semantic dementia and fv-FTD patients showed similar patterns across time on autobiographical memory, as in our study they failed to show any comparable temporal gradient for the two groups (step-like effect and flat gradient, respectively). Accordingly, they refuted the idea that the profile they observed in semantic dementia was due to a deficit of strategic retrieval. Secondly, Moscovitch and Nadel (1999a) propose that remote performances of these patients may be limited by their verbal skill deficit, rather than a storage deficit (Westmacott *et al.*, 2001). In effect, the R responses (relative to the other measures), which were spared in our patients with semantic dementia,

did not require high narrative competency. Thirdly, these authors also propose that the loss of remote autobiographical memories in semantic dementia may reflect ‘the extent that the semantic information that is lost is either part of the memory trace or is needed to access it’. In contrast, recent memories would be preserved because they are more perceptual than semantic in nature. Recent results in semantic dementia support this latter supposition (Hodges and Graham, 2001; Nestor *et al.*, 2002; Simons *et al.*, 2002).

Therefore, as far as the semantic dementia patients (where the temporal neocortex is affected) in particular are concerned and, as Nestor *et al.* (2002) recently pointed out, the profile of autobiographical memory (i.e. reversed temporal gradient or step-like effect) is consistent with both the standard and the multiple trace consolidation models—the former evoking a deficit of stored information situated in the temporal neocortex and the latter evoking a deficit of access as the temporal neocortex is needed to gain access to autobiographical memories. The MTT, however, accounts more fully for the differing patterns of impairment observed in our three patient groups than the standard model.

It is worth mentioning that although the models of consolidation (especially the MTT in our case) provide powerful explanations of many neuropsychological data, they need to be more specific when it comes to the functional neuroanatomy of episodic memory (Desgranges *et al.*, 1998b; Cabeza and Nyberg, 2000; Bernard *et al.*, 2001), and in particular, to the neocortical involvement in autobiographical memory retrieval highlighted by neuropsychological data and, more recently, by neuroimaging data. These studies have emphasized the heterogeneity of the sites of lesions responsible for retrograde amnesia (Conway and Fthenaki, 2000; Kopelman and Kapur, 2001). More especially, studies of focal autobiographical retrograde amnesia have highlighted the critical role of the frontal and anterior temporal lobe and the occipital lobe (for review, see Rubin and Greenberg, 1998; Kapur, 2000; Kopelman, 2000b). This heterogeneity shows that remote memory is widely distributed across the brain and that all these areas play a critical role in performance, especially the right frontotemporal anterior lobe in episodic autobiographical memory (Markowitsch, 1995; Calabrese *et al.*, 1996; Kroll *et al.*, 1997; Levine *et al.*, 1998). Functional neuroimaging studies of autobiographical memory have also revealed the existence of a widespread cerebral network involving the prefrontal cortex, medial and lateral temporal cortex, retrosplenial and posterior cingulate cortex (see Maguire, 2001 for a review). The different sites of atrophy in our three patient groups are particularly relevant to these networks. For instance, the posterior cingulate cortex, which is involved in autobiographical memory retrieval (Maddock *et al.*, 2001) is damaged in Alzheimer’s disease at a very early stage of dementia (Minoshima *et al.*, 1997; Chételat *et al.*, 2003a, b).

Interestingly, a recent constructive model of autobiographical memory (Conway and Pleydell-Pearce, 2000; Conway and Fthenaki, 2000; Conway, 2001; see also

Hodges and McCarthy, 1995) assumes that a complex retrieval process relying on the frontal lobe allows one to access sensory/perceptual event-specific knowledge (situated in the posterior regions, especially occipital region in visual imagery) through the personal knowledge base (lifetime periods and general events situated in the fronto-temporal anterior regions). Within this framework, autobiographical memory loss can result from different types of pathological process involving either diffuse widespread cortical damage to separate regions or focal damage to one of the critical regions as well as damage to their interconnections. Hence, in addition to the impairment of the MTL (regardless of model), the profile of the Alzheimer's disease patients may also be determined by a frontal lobe dysfunction responsible for a deficit in access to the source of remote memories (Greene *et al.*, 1995) as suggested by their working memory and executive difficulties (observed in the general cognitive assessment). The profile of semantic dementia may be determined by a deficit of access (Piolino *et al.*, 2003), as the impairment of personal semantic memory subtended by anterior temporal atrophy may prevent access to episodic details (i.e. phenomenological registry, Conway, 1992). The reversed temporal gradient we observed may reflect the increasing importance of the personal semantic component for reconstructing autobiographical memory over time (Moscovitch and Nadel, 1999a; Piolino *et al.*, 2002). Furthermore, in keeping with the impaired performances of fv-FTD patients on tests of frontal/executive function, their profile may be easily interpreted by a dysfunction of the mechanisms engaged in the active process of retrieval (i.e. strategic, self-initiated) from long-term memory involving connections with the frontal lobe.

Based on this idea that autobiographical memory is multifaceted and retrieved via a series of activation linking all the components of an autobiographical memory experience, it is conceivable that the loss of one of the critical parts of the network (i.e. strategic process, conceptual knowledge, visual or multi-modal imagery) may bring the activation process to a standstill, resulting in poor autobiographical memory retrieval (see Nestor *et al.*, 2002). The MTL (regardless of model) acts as an index to the neocortical elements needed to provide details of the experiences. According to the standard model, after a few years, the patterns of autobiographical retrograde amnesia depend solely on neocortically-based memory traces. According to the MTT, however, the patterns of episodic retrograde amnesia continue to depend on the medial-neocortical ensemble, regardless of the time period. Hence, as argued by Moscovitch and Nadel (1999a), the pattern of remote and recent memory loss depends 'very much on the type of information represented by the structures that are damaged' in the neocortex (see Kitchener and Hodges, 1999; Piolino *et al.*, 2003). Further work needs to be done, if we are to gain a better understanding of the role of the medial temporal-neocortical ensemble in the retrieval of autobiographical memory.

In summary, our results highlight mainly the existence of severe autobiographical amnesia regardless of the neurodegenerative disease, though with contrasting profiles: Ribot's gradient in Alzheimer's disease, reverse gradient in semantic dementia and no clear gradient in fv-FTD. This triple dissociation strengthens the assumption that the nature of retrograde amnesia depends on the locus of cerebral dysfunction. Moreover, this study documents for the first time the differential impairment in strictly episodic autobiographical amnesia and the sense of remembering in Alzheimer's disease, semantic dementia and fv-FTD pathologies. Our results propose new insights that question the 'standard model' of memory consolidation and support the view that mechanisms of consolidation differ according to the kind of knowledge being assessed (episodic and semantic memories), in accordance with the alternative MTT. The phenomenal experience of remembering is at the core of the debate on cerebral structures involved in remote autobiographical memories.

Acknowledgements

We wish to thank E. Wiles-Portier and Dr A. Young for reviewing the English style and Dr D. Clarys, M. Josset, J. Léger and M. Perron for their help in carrying out the neuropsychological examinations of the patients.

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Received November 7, 2002. Revised, April 28, 2003.

Accepted April 29, 2003