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Update in neurosciences

Recognition memory and the medial temporal lobe: From monkey research to human pathology

Mémoire de reconnaissance et lobe temporal médian : de la recherche chez le singe à la pathologie chez l'homme

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ABSTRACT

This review provides a historical overview of decades of research on recognition memory, the process that allows both humans and animals to tell familiar from novel items. The emphasis is put on how monkey research improved our understanding of the medial temporal lobe (MTL) role and how tasks designed for monkeys influenced research in humans. The story starts in the early 1950s. Back then, memory was not a fashionable scientific topic. It was viewed as a function of the whole brain and not of specialized brain areas. All that changed in 1957–1958 when Brenda Milner, a neuropsychologist from Montreal, described patient H.M. He forgot all events as he lived them despite a fully preserved intelligence. He had received a MTL resection to relieve epilepsy. H.M. (1926–2008) would become the most influential patient in brain science. Which structures among those included in H.M.'s large lesion were important for recognition memory could not be evaluated in humans. It was gradually understood only after the successful development of a monkey model of human amnesia by Mishkin in 1978. Selective lesions and two behavioral tasks, delayed nonmatching-to-sample and visual paired comparison, were used to distinguish the contribution of the hippocampus from that of adjacent cortical areas. Driven by findings in non-human primates, human research on recognition memory is now trying to solve the question of whether the different structures composing MTL contributes to familiarity and recollection, the two possible forms taken by recognition. We described in particular two French patients, FRG and JMG, whose deficits support the currently dominant model attributing to the perirhinal cortex a critical role in recognition memory. Research on recognition memory has implications for the clinician as it may help understanding the cognitive deficits observed in different diseases. An illustration of such approach, linking basic and applied research, is provided for Alzheimer's disease.

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RÉSUMÉ

Cette revue propose un aperçu de 50 ans de recherche sur la mémoire de reconnaissance en mettant l'accent sur ce que la recherche et les tâches développées chez le singe ont apporté à notre compréhension du rôle du lobe temporal médian (LTM). Au début des années 1950, la mémoire n'était pas très en vogue; il semblait acquis qu'elle était une fonction distribuée dans le cerveau entier. Tout change en 1957–1958 quand Brenda Milner rapporte le cas d'un patient qui oubliait tous les événements qu'il vivait suite à une résection du LTM pour soulager son épilepsie. H.M. (1926–2008) deviendra le patient le plus influent des neurosciences. Quelles structures parmi celles détruites chez H.M. sont importantes pour la mémoire de reconnaissance ? Cette question a été lentement résolue après le développement d'un modèle singe de l'amnésie humaine par Mishkin en 1978. Des lésions sélectives et deux tâches comportementales ont été utilisées pour distinguer la contribution de l'hippocampe de celle des régions corticales adjacentes. La recherche humaine essaie maintenant de déterminer si les différents composants du LTM contribuent de la même façon aux deux formes de reconnaissance : la familiarité et la recollection. Nous décrivons en particulier deux patients français, FRG et JMG, dont les déficits soutiennent le modèle actuellement dominant attribuant au cortex perirhinal un rôle critique dans la mémoire de reconnaissance. La recherche sur la mémoire de reconnaissance a également des conséquences sur la compréhension des troubles cognitifs observés dans différentes pathologies, en particulier dans la maladie d'Alzheimer, comme illustré en fin de cette revue.

Recognition and recall are memory processes allowing conscious access to information previously encoded and stored in long-term memory (Tulving and Thomson, 1973). Recall is the self-organized retrieval of an event from long-term memory without any help (free recall) or based on partial information (cued recall). The tip-of-the-tongue phenomenon is a typical recall failure. Recognition, by contrast, is the mere decision that a currently present person, object, place, or event has been encountered or experienced before; hence, it is often, though not always, more efficient than recall.

Recall and recognition are the retrieval processes of a specific memory system, termed declarative, which includes both memory for personal events and memory for facts about the world (Squire, 2004). This system is distinct, functionally and anatomically, from the procedural, implicit, habit memory system, which simply expresses previously acquired skills through performance. Unlike procedural learning, which entails a lengthy acquisition phase, new information is rapidly committed to declarative memory (Mishkin et al., 1984). Accordingly, a characteristic common to all recognition memory tasks is the use of a single exposure to the stimuli to be memorized. The effect of this single exposure is then typically evaluated by asking subjects, humans or animals, to choose between two items the one they have been exposed to earlier.

Declarative memory is the system that is selectively disrupted in human amnesia (Squire and Wixted, 2011). This syndrome leads in most patients to dense impairments in both recall and recognition, but relative sparing of recognition over recall has nevertheless been observed in a few amnesic patients. Recognition tasks are therefore markers of declarative memory, crucial for understanding human amnesia, with the reserve that they cannot provide insights into all forms of declarative memory, but only into a subset of declarative memory processes.

Recognition itself is not a single process as it can yield two different outcomes: either a pure familiarity/novelty judgment or a full event recollection akin to recall (for a review see Yonelinas, 2002). The former is epitomized by what is known as the "butcher-on-the-bus phenomenon" (Mandler, 1980): someone seen in an atypical context that we feel is familiar while failing to remember any information whatsoever about him or her. The latter consists, like recall, in remembering the information plus the spatiotemporal context of the latest episode in which it was encountered, e.g., in remembering the butcher as well as its tiny shop down the block and the fantastic T-bone steaks he sold you last Saturday. Determining whether familiarity and recollection are two independent processes subserved by different brain structures or can be accounted for more parsimoniously by a single process is a challenge to current research. Models and proposals abound in this domain and the last few years have not been exceptions to this trend.

The aim of this article is to provide a short historical overview of decades of research on recognition memory. A parallel is drawn between research in the animal and research in the human. The emphasis is put on how monkey research improved our understanding of the medial temporal lobe (MTL) role and how recognition memory tasks designed for monkeys influenced research in humans. Two implications for the clinician are described. First, we describe two French patients, FRG and JMG, whose deficits support monkey data attributing to the perirhinal cortex a critical role in recognition memory. Then we illustrate how research on recognition memory helped understanding the cognitive deficits accompanying neurodegenerative diseases through the example of Alzheimer's disease (AD).

1. Human amnesia, the medial temporal lobe and patient H.M.

In 1950, Karl Lashley published the results of 30 years of lesions studies in rats spent "In Search of the Engram" only to conclude that "It is not possible to demonstrate the isolated localization of a memory trace anywhere within the nervous system". Thus, the theory of centralized memory storage in the brain had been laid to rest. At about this same time, however, quite different results emerged from Wilder Penfield's investigations in epileptic patients about to undergo surgical removal of their epileptic foci (Penfield and Perot, 1963). Pre-surgery stimulation of some cortical areas would repeatedly elicit detailed memories in the awake patient and subsequent unilateral temporal lobe resections could result in mild memory impairments. It is thus not surprising that we owe to one of Penfield's collaborator, Brenda Milner, the description of the landmark case H.M. which, for more than 50 years now, drives the study of memory and its neural underpinnings (Scoville and Milner, 1957).

In 1953, Henry Molaison (1926–2008) was treated for intractable epilepsy by the bilateral removal of the MTL. The result of this surgery was a devastating global (non-modality specific) anterograde amnesia, with a milder retrograde amnesia disrupting events close to the time of his operation without affecting his childhood memories. This profound deficit made the skill learning capabilities that were later proved to be retained by H.M all the more remarkable. H.M.'s case thus established three important points:

- the MTL is required to encode some new memories, but some memory functions remain intact after MTL damage;
- because some past memories survived, the MTL is not the permanent storage site of long-term memory;
- to the extent it is involved in retrieval, this role must be time-limited as well.

The now prevailing concept of multiple memory systems comes directly from H.M. and other patients suffering like him from global anterograde amnesia.

The MTL is a large region including two deep structures, the amygdala and hippocampus, which are wrapped rostrally by the entorhinal and perirhinal cortices, and caudally by the parahippocampal cortex (Fig. 1). As estimated by William Scoville at the time of surgery, H.M. removal involved most of these structures. Why then was H.M.'s memory deficit attributed to the sole hippocampal damage? The original study by Scoville and Milner (1957) concerned 30 patients with bilateral temporal lobectomy. The three patients, who developed the amnesic syndrome, including H.M., had estimated excisions that extended sufficiently posterior to include a large portion of the hippocampus in addition to the amygdala. A subsequent study by Penfield and Milner (1958) involved 90 patients with temporal lobectomies that, although posterior enough to damage a large portion of the hippocampus, were only unilateral. Two patients nevertheless developed the amnesic syndrome. Autopsy findings from one of this patient revealed a shrunken and necrotic hippocampus in the unoperated temporal lobe without any obvious damage to neighboring structures (Penfield and Mathieson, 1974). A moderate amnesic syndrome was later described in a patient who suffered an ischemic event yielding a bilateral medial temporal damage thought at the time to be restricted to the CA1 field of the hippocampus. These are the main findings that imposed the idea of the hippocampus as the structure whose bilateral damage was responsible for human amnesia. What was not immediately forthcoming was similar evidence from the animal literature.

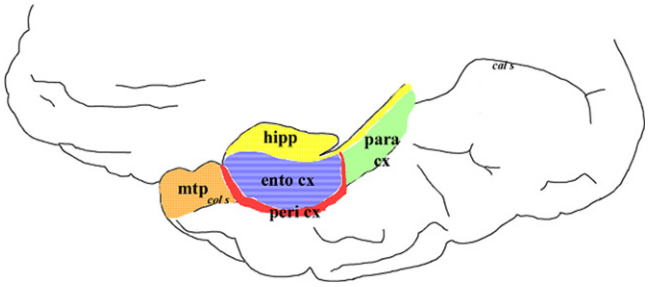

Fig. 1 – Medial view of the right temporal lobe, along with a schematic representation of the various medial temporal lobe structures. ento cx: entorhinal cortex; para cx: parahippocampal cortex; peri cx: perirhinal cortex; mtp: medial temporopolar cortex; col s: collateral sulcus; hipp: hippocampus; cal s: calcarine sulcus. The posterior limits of the hippocampus and parahippocampal cortex are not represented.
Adapted from Barbeau et al., 2004b (see Frankó et al., 2012 for methods of identification of these medial temporal structures on magnetic resonance images).

2. In search of an animal model of human amnesia

Contrasting with the devastating effect of MTL damage on human memory, damage to the hippocampus in monkeys initially appeared to have very limited and somewhat specific effects on monkey memory. For some time it appeared that there was no comparison between humans and monkeys in spite of the high degree of anatomical homology between the two species with respect to the MTL structures. In particular, H.M.'s failure on recognition memory tasks, revealed in a seminal study by Brenda Milner (1972), could not be evidenced in monkeys.

In 1975, Mishkin and Delacour modified the matching-to-sample memory task developed by Gaffan in 1974 so that it could readily be learned by monkeys, while being closer to tests of human recognition memory, known as trial-unique. They use a nonmatching rather than a matching rule to take advantage of monkeys' natural attraction to novelty (Fig. 2). To better approximate the recognition tasks used in humans, they used large pools of stimuli, creating a version of the task with "trial-unique" stimuli. That is, rather than requiring the monkey to remember which stimulus had been seen most recently (recency memory), the new version simply required the monkey to indicate which stimulus was novel, while

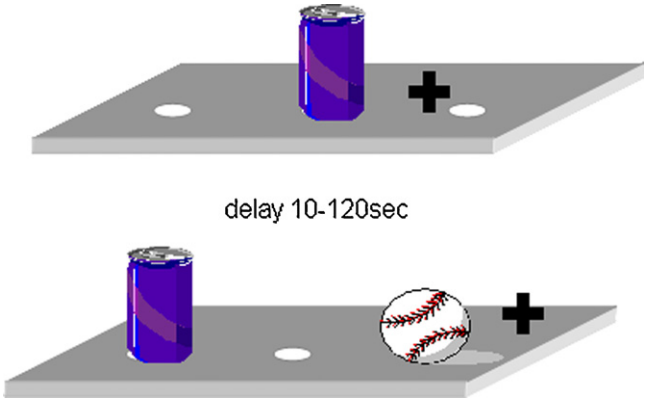

Fig. 2 – In the delayed nonmatching-to-sample (DNMS) task, a trial comprises two phases. First, a sample is presented over the central well of the test tray; it conceals a food treat that the monkey can retrieve by displacing the object. Then, a choice is proposed between the same object and a new one that the animal has never seen before. The monkey must displace the novel object to get another treat. Recognition memory is evaluated by extending the retention delays between sample and choice (typically up to 120 s) or by increasing the number of objects to be remembered (not illustrated).

avoiding the previously seen other stimulus (recognition memory). Another crucial change was to combine this new task with extensive MTL ablations similar to that sustained by H.M., that is, encompassing both the amygdala and the hippocampal regions. Mishkin thus demonstrated for the first time in 1978 that, whereas "amygdalectomy" or "hippocampectomy" alone produce mild impairments at best, combined lesions, effectively replicating H.M.'s damage, produce a severe impairment. As delayed nonmatching-to-sample with trial-unique stimuli (DNMS) was the first task to successfully demonstrate a recognition memory deficit in monkeys accurately modeling that produces by human amnesia, it became the benchmark task in monkey research for about 15 years.

DNMS is simple in that monkeys learn to displace junk objects to obtain a hidden food reward. An opaque screen separates the animal from a testing tray containing three equidistant food wells. The wells can be covered with junk objects, and can be either baited or empty. Training takes place in two phases for each trial: sample and choice. During the sample phase, a single object covers the central food well and when displaced, a food reward can be retrieved. The screen is then lowered and the now-familiar sample object is moved to cover a lateral well (empty) while a novel object covers the opposite lateral well (baited). After 5–10 s, the screen is raised and the monkey must choose one of the objects. If the animal remembers the sample object, and correctly choose the novel item, then the food reward can be retrieved. When the animal reliably masters the nonmatching rule, memory can be further manipulated by:

- introducing variable delays between the sample and choice phases (generally from 30 s to 40 min), occupied or not with interfering tasks;
- increasing the number of items to be remembered (list learning, generally from 3 to 10 objects).

The early work by Mishkin and others confirmed that large lesions to the MTL dramatically impair performance while sparing performance on tasks such as visual discrimination learning in which monkeys learn a set of 20 concurrent discrimination problems that are presented only once per day, thus with 24-hour delays. These results match the spared and impaired performance capabilities of amnesic patients such as H.M., who cannot retain new information for more than a few seconds without active rehearsal, but can improve over many trials to perform tasks such as mirror drawing. However, as a measure of combined "*amygdalo-hippocampal*" memory function, the results from DNMS task were soon called into question.

3. DNMS: revealing the importance of underlying cortex

Having a monkey model of human amnesia made it possible to parse out the individual contributions of MTL structures to recognition memory. At the end of the 1980s, Zola-Morgan et al. raised for the first time the possibility that the cortical damage included in the so-called "*amygdalo-hippocampal*" lesions did contribute to the severe DNMS impairment observed by Mishkin (1978). These authors first showed that radio-frequency lesions of the amygdala sparing adjacent cortex fail to exacerbate the mild memory impairment produced by hippocampal damage. Then, they demonstrated that ablations restricted to the perirhinal and parahippocampal cortices suffice to severely disrupt DNMS performance (Zola-Morgan et al., 1989a, 1989b). Meunier et al. (1993) later demonstrated that removing the perirhinal and entorhinal areas (collectively referred to as 'rhinal' cortex) devastates DNMS performance in monkeys, producing as large an impairment as the combined "*amygdalo-hippocampal*" lesion (Fig. 3).

The rhinal cortex is now unanimously viewed as a key substrate of primates' recognition memory. What remains a matter of debate is the hippocampus contribution. Even the use of cell-selective neurotoxic lesions has not entirely solved this question. In 1998, Murray and Mishkin showed that monkeys with such neurotoxic, fiber-sparing damage to the hippocampus and amygdala showed normal DNMS performance out to 2-minute delays. Nor were they impaired on lists of 40 items. On the other hand, Zola et al. (2000) found that hippocampal damage, whether produced by neurotoxin, radio-frequency, or forebrain ischemia, impaired DNMS performance at delays of 10 minutes and beyond. For hippocampal damage resulting from ischemia, this result has been called into question as ischemia, which was thought to damage only a single hippocampal cell field (CA1), is now known to yield widespread damage (see for review Bachevalier and Meunier, 1996), but the debate is still open for other lesion type. Nemanic et al. (2004) did find a DNMS deficit after neurotoxic lesions but only when combining a long 10-min delay to a distraction by removing the animal from the testing room. So the debate is not closed yet, but there is consensus

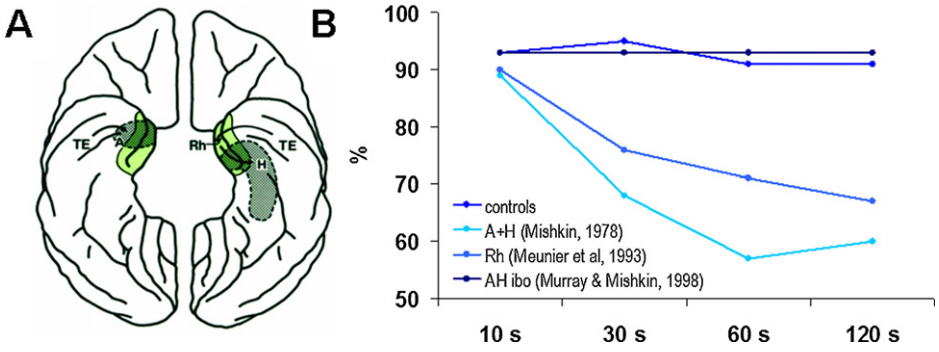

Fig. 3 – A. Ventral view of the monkey brain showing why aspiration of the inner medial temporal lobe structures: the amygala and hippocampus (A and H, shown in transparency) necessarily led to complete removal of the rhinal areas (Rh, purple). B. Main results from Mishkin and collaborators showing that the deficit described in 1978 after large "AH" lesions mimicking H.M.'s resection was essentially due to rhinal damage (Rh, Meunier et al., 1993) and was not reproduced at all by neurotoxic AH lesions sparing rhinal areas (Murray and Mishkin, 1998).

that, at most, the effect of selective hippocampal damage on DNMS is mild and restricted to long delays.

In any case, lesions restricted to the sole perirhinal cortex clearly disrupt DNMS performance much more severely than hippocampal damage, even at very short delays and without any distraction (Meunier et al., 1993, 1996). Hippocampal damage, by contrast, leaves short-term memory intact on this task.

4. Visual paired comparison: revealing hippocampal contribution

The visual paired comparison task (VPC) is coming from the human developmental literature and has been extensively used to study the memory capacities of human infants who, like monkeys, are characterized by their lack of language. Like DNMS, VPC takes advantage of monkeys' natural preference for novelty. It also utilizes a familiarization phase and a choice phase, but the task demands are quite different. Contrary to DNMS, VPC requires neither rule learning, nor forced-choices between two objects to obtain a reward. For VPC, monkeys passively view a visual stimulus, typically a black/white image, and are allowed to look at it for a sufficient period to show habituation (i.e., they cease visual exploration). This familiarization period may range from 15 to 30 s of looking time. At this point, the image disappears and after a variable delay period (as brief as 1 s) the image reappears on the screen, side-by-side with a novel image. Monkeys and humans naturally prefer to look at (explore) the stimulus they have not yet seen (novelty preference), thus we infer that they remember the familiar stimulus. Given that the subject is not actively performing a task, it should not be surprising that performance levels on VPC are much lower than on DNMS, where animals are trained to a 90% correct criterion. With VPC, typical novelty preference is in the range of 65–70% preference for novelty, but this effect is reliable.

The difference between the two tasks is their relative sensitivity to medial temporal damage, in general, and hippocampal damage, in particular. Two studies have directly compared VPC and DNMS in the same hippocampectomized monkeys (Zola et al., 2000; Nemanic et al., 2004; see below for similar results in humans). The specific delays yielding a severe VPC impairment varied across studies: 60 s or more in Nemanic et al. (2004), 10 s or more in Zola et al. (2000; group RF2) but, in both cases, DNMS performance at the very same delays in the very same subjects was found to be spared, 10-min delays being necessary for a clear-cut DNMS deficit to emerge. Thus, VPC is clearly more sensitive than DNMS. In a recent study, Zeamer et al. (2011) demonstrated that this greater sensitivity stems, at least in part, from the type of stimuli used for VPC as hippocampectomized monkeys have more trouble memorizing the black and white pictures typically used for VPC than the colored objects typically used for DNMS (Fig. 4).

Similar to DNMS, however, damage to the medial temporal cortical areas produces impairments at shorter delays (~30 s for parahippocampal gyrus, and ~10 s for perirhinal cortex; Nemanic et al., 2004). Thus, though the sensitivity may be greater in detecting recognition memory deficits in the VPC task, the contribution of the different MTL structures maintains a similar relationship to each other; that is, perirhinal contributes in the initial encoding and short-term retention of visual stimuli, whereas parahippocampal areas TH/TF and the hippocampus are required for longer retention. Thus, the two main measures of recognition memory both outline the same relative contribution of the different medial temporal structures to recognition memory.

5. Familiarity and recollection in animals

Although familiarity and recollection are at first phenomenological phenomena, i.e. related to special types of awareness, that have been widely studied in humans, they are also viewed by some authors as specific memory processes. An important aim has been to design methods to assess these processes in animals. This has been achieved these last years through the analysis of receiver operating characteristics (ROC) in both rodents (Fortin et al., 2004; Sauvage et al., 2008) and monkeys (Guderian et al., 2011). Briefly, ROC analyses are based on the confidence with which answers are provided

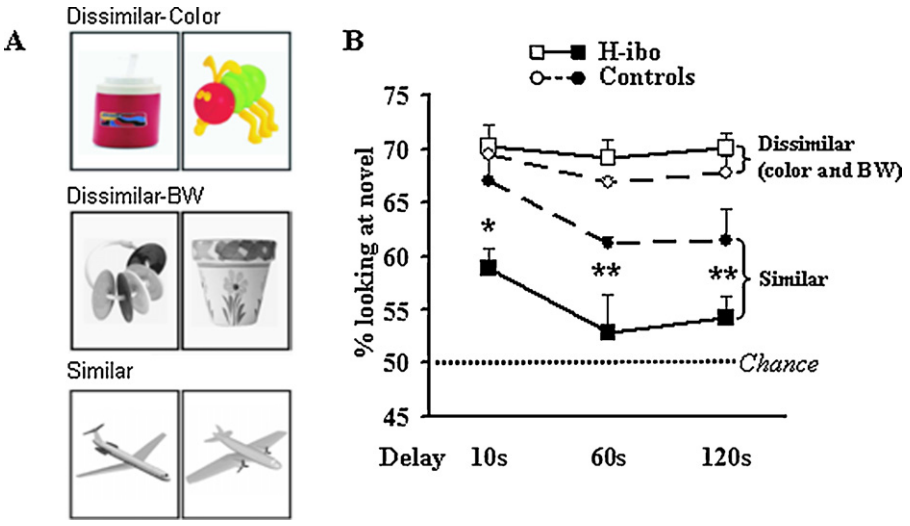

Fig. 4 – Recognition memory for dissimilar (color or black-and-white) vs. similar stimuli in monkeys with selective hippocampal lesions as measured by the visual paired comparison (VPC) task. A. Examples of the pairs of stimuli used. B. Percent of time spent looking at the novel stimulus (mean + SEM) in monkeys with sham operations (Controls) or neurotoxic hippocampal lesions (H-ibo) at each of the three delays tested. Although lesioned monkeys perform normally when stimuli are easy to discriminate, they are impaired when stimuli are similar ($P = 0.06$, $^{**}P \leq 0.04$). The fact that VPC typically uses black-and-white images (instead of the colorful objects used in DNMS) could therefore explain its greater sensitivity to hippocampal lesions.
Adapted from Zeamer et al., 2011.

(i.e. from sure ''old'' to sure ''new'') under the assumption that recollection is an all-or-none process that will lead to a high number of hits and a small number of false-alarms and that both recollection and familiarity are independent processes. A model is applied on the data (e.g. the Dual-Process Signal Detection model, DPSD, as proposed by Yonelinas in 1994) to extrapolate a quantitative measure of familiarity and recollection. Findings in the animal have supported the idea that familiarity depend on the perirhinal cortex or its equivalent, whereas recollection depends on the hippocampus, in agreement with a strict view of the anatomo-functional fractionation of the MTL (Eichenbaum et al., 2012). Interestingly, a recent study reported a selective impairment of familiarity following amygdala lesions in the rodent, raising the possibility that familiarity would depend on other structures than the perirhinal cortex only (Farovik et al., 2011). Several arguments have been proposed against the use of such method and model (Wixted and Squire, 2008, 2010), but these studies have opened up an interesting avenue into the study of these processes at the neuronal level in the animal.

6. Recognition memory in human brain-damaged patients

Recognition memory in the human is a highly efficient cognitive ability. Studies suggest that humans can encode thousands of stimuli in a few hours (Standing, 1973; Bogacz et al., 2001; Brady et al., 2008) and can recognize them rapidly and reliably in as little as 370 ms post-stimulus (Besson et al., in press).

Human amnesia has, by and large, been tested with numerous tasks that are quite different from those used with animals. Thus, differences in the nature or extent of impairments between animal models and the human impairment may be due to task differences, to lesion differences, to evolutionary forces, in addition to the lack of language capabilities. This makes it important to test humans on animal memory tasks both to validate the behavioral assays, and better understand specific impairments in human patients. Regarding the lesion differences, the recent reports of patients with selective damage to individual components of the MTL provides an opportunity to test specific memory functions in humans with similarly selective damage, to compare the results with those from other species, and eventually, may inform the assessment of human patients.

Tests of human amnesic patients on animal tests of recognition, while relatively few, are largely in agreement with the animal findings when large temporal lobe lesions were used. For example, Squire et al. (1988) reported that a group of patients whose presumed damage was either diencephalic (Korsakoff's patients) or hippocampal (ischemic/anoxic patients) were severely impaired on the DNMS task, similar to the initial monkey studies (Mishkin, 1978). In addition, recognition memory impairments have been demonstrated on the VPC task, and, as in animals, these impairments are often larger than those obtained from matching or nonmatching tasks. Direct comparisons of VPC and delayed matching-to-sample (DMS) performance have been investigated in human amnesic patient YR by Pascalis et al. (2004). Patient YR became amnesic after a possible ischemic infarct, resulting in reduced hippocampal volume and no other obvious pathology as

measured by MRI. This patient had previously shown impaired recall, but intact recognition on standard human memory tests. She also demonstrated severe impairments in memory on VPC demonstrating preference for novelty at the 0 s delay only. At the longer delays of 5 and 10 s, her performance fell to chance. By contrast, as described above, her performance was as good as controls on the DMS task with delays up to 30 s (see also Pascalis et al., 2009 for additional results regarding the VPC and YR).

Driven by findings in non-human primates (Meunier et al., 1993; Chavoix et al., 2002), the human literature on recognition memory is now trying to solve the question of the specific contribution of the different structures composing the MTL. Aggleton and Shaw (1996) were the first to notice that some amnesic patients could show impaired recall (by definition since they are amnesic), *but* preserved recognition. This observation was followed by the report by Vargha-Khadem et al. (1997) of the case of three adolescents who suffered from developmental amnesia following relatively isolated lesions to the hippocampus bilaterally. All were severely amnesic, were lost in time and space but performed virtually normally on tasks of verbal and visual recognition memory. In the following years, several cases were reported of amnesic patients following isolated hippocampal lesions acquired during adulthood who performed relatively normally on tasks of recognition memory (case YR, Mayes et al., 2002; case MR, Bastin et al., 2004; case KN, Aggleton et al., 2005; case FRG, Barbeau et al., 2005). Group studies appeared to support these findings (Turriziani et al., 2004). The reverse dissociation was also studied, although such reverse dissociation appears rather rare. Barbeau et al. (2011) published the case of JMG, who sustained extremely large MTL lesions bilaterally preserving the right hippocampus. This patient was not amnesic but failed recognition memory tasks (see below). All in all, these studies appear to converge on a rather simple, and segregated, account of the anatomo-functional organisation of MTL structures holding that the hippocampus would not be a critical structure for recognition while the perirhinal cortex would perform some critical computation necessary for this kind of task.

This model has been challenged by several studies disputing the idea that recall would be more impaired than recognition in patients with isolated hippocampal lesions (Reed and Squire, 1997; Manns and Squire, 1999; Manns et al., 2003; Kopelman et al., 2007). Yet, for the time being, this model remains dominant as it does account for most non-human and human data.

7. A real-life story of a double-dissociation

Here, we detail the case of two patients, FRG and JMG, who both sustained large MTL lesions following herpex simplex encephalitis but show a double anatomo-functional dissociation. In doing so, we illustrate the importance of carrying out detailed, hypothesis-based, research in brain-injured patients. It also illustrates how basic research can provide a framework that can be used to drive clinical assessment.

FRG was 44 at the time of her disease and she was referred to us 4 years later (AP–HP Timone, Marseilles). Her cerebral MRI showed that all left medial temporal structures had been totally destroyed. In the right hemisphere, the amygdala and the hippocampus had completely disappeared also, but anterior subhippocampal structures, in particular the perirhinal cortex, were spared (Fig. 5). FRG was severely amnesic (delayed QM from the WMS-R: 56, mean = 100, SD = 15). She was disorientated in time and space, became forgetful, and, having lost her autonomy, had to quit her job.

We gave FRG 18 visual recognition memory tasks using different types of stimuli and paradigms (Barbeau et al., 2005). The results of the tests were expressed as Z-scores. FRG demonstrated normal performance in 14 of the 18 visual recognition memory tasks (> -2 SD), with a mean Z-score for the 18 tasks of -0.8. Her performance was therefore within the normal range of control subjects. Her very long-term (1 week) visual recognition memory was within normal range. We sought to confirm whether this good performance was related to the ease of the tasks. Indeed, it could have been that FRG was only successful in the easiest tasks, and failed in the more difficult tasks. We calculated a difficulty index for each tasks, and established the correlation between performance expressed as a Z-score for each of the tasks and its difficulty index. FRG tended to do better than the control subjects on the more difficult tasks. Consequently, this patient, who presented severe hippocampal lesions and a serious associated amnesic syndrome, showed normal performance on visual recognition

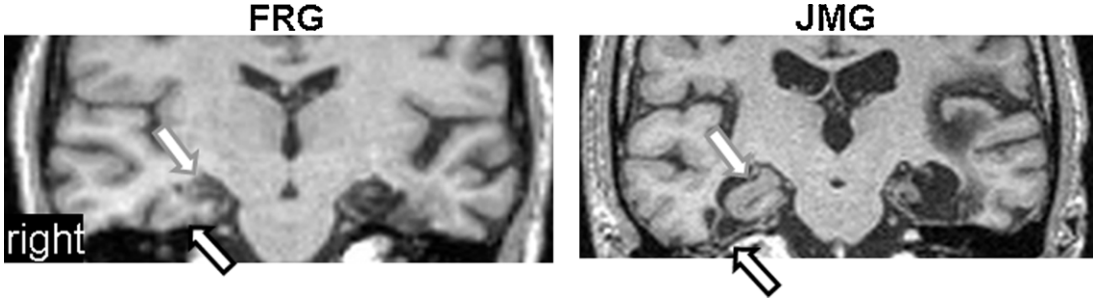

Fig. 5 – Coronal views of FRG and JMG medial temporal lobe structures. Left medial temporal lobe structures are completely damaged in both patients. In the right hemisphere, FRG's perirhinal cortex is preserved (black arrow) while the hippocampus is damaged (grey arrow). In JMG in contrast, the right perirhinal cortex is damaged while his right hippocampus is preserved.

memory tasks. Preserved visual recognition memory was related to the preservation of her right perirhinal cortex.

A few years later, patient JMG, aged 54, was referred to our centre in CHU Purpan, Toulouse. His cerebral lesions on MRI were considerable on the left and affected almost all of the temporal lobe (Fig. 5). They were also substantial on the right, and actually more important than those of H.M. across both hemispheres. However, and surprisingly, while all subhippocampal structures were damaged, the right hippocampus was spared. The lesion profiles of patients JMG and FRG were therefore totally opposite and showed a double anatomical dissociation. We sought to assess whether this anatomical dissociation translated into a functional dissociation (Barbeau et al., 2011). Both JMG and FRG suffered from the same herpetic encephalitis pathology. They were of a similar age (48 and 54 years old) and of a similar IQ. It was therefore possible to compare them on the same set of tasks using the same group of control subjects.

JMG performed well on visual free recall (mean Z-score = −0.3). Actually, he did not suffer from an amnesic syndrome, despite the size of his lesions. His memory was subnormal and inferior to that of control subjects, but remained compatible with normal life in contrast to FRG. However, unlike FRG, JMG demonstrated very poor performance on the 18 visual recognition memory tasks (mean Z-score = −4.8). Importantly, JMG's low performance could not be ascribed to visual difficulties or attentional problems. A double functional dissociation between FRG and JMG was therefore evidenced.

In summary, we report a double anatomo-functional dissociation between two patients demonstrating that visual recognition memory critically relies on right subhippocampal structures in the human. This double-dissociation greatly strengthens and extends the findings of previous studies which have reported single-dissociations in patients with isolated lesions to the hippocampus (Holdstock et al., 2000; Mayes et al., 2002; Bastin et al., 2004; Aggleton et al., 2005) and appear to match findings in the non-human primates.

8. Familiarity and recognition

Attempts to model the psychological processes subtending performance on recognition memory tasks started very early on (Kintsch, 1967; Mandler et al., 1969; Juola et al., 1971)[1]. Later, several recognition memory paradigms were developed to assess familiarity *versus* recollection, such as the Remember/Know procedure, the Process Dissociation Procedure, ROC curve analyses, Speed-Accuracy Trade-off, etc. (reviewed in Yonelinas, 2002). As for models, the most well-known is the Dual-Process Signal Detection model (DPSD) proposed by Yonelinas first in 1994. DPSD models familiarity in the context of the Signal Detection Theory, and view recollection as a threshold process. It relies on the assumption that familiarity and recollection are two independent processes, each with its own neural substrate. This model is supported by empirical data reporting impaired recollection following damage to the hippocampus (Yonelinas, 2002; Turriziani et al., 2008), and impaired familiarity with intact recollection on verbal recognition memory tasks following surgical removal of the left anterior subhippocampal structures (Bowles et al., 2007).

Though dominant, the DPSD model is not undisputed (Wixted and Squire, 2004). The alternative view is that familiarity and recollection form a single process (Wixted, 2007; Wixted and Mickes, 2010) sharing the same neural substrate (Cowell et al., 2010). In support of this view, Wais et al. (2006) have reported impaired recollection *and* familiarity in humans after isolated damage to the hippocampus. This has led Squire et al. (2007) to offer an alternative account of the neural bases of recognition memory. It postulates that subhippocampal structures *and* the hippocampus all support familiarity and recollection, the former supporting weak forms of familiarity and recollection (i.e. weak memories), the latter supporting strong forms of recollection (i.e. strong memories). This proposal is anti-module and argues against mapping specific cognitive processes on specific MTL structures.

All in all, familiarity and recollection have remained elusive phenomena and it has been difficult to disambiguate phenomenological, psychological and neural levels of processing despite a few decades of research (Voss and Paller, 2010). However, methodological advances (ROC analyses in animals, new psychological models and proposals, single-units recording in humans, etc.) and much effort in the field should solve the current debate in the near future.

Of course, such basic research, i.e. trying to understand the cognitive processes taking place in the normal subject through the study of brain lesions, can be applied to the understanding of the cognitive deficits thought to occur in different pathologies. In the next section, we illustrate this approach for AD.

9. Recognition memory and pathology: MCI and Alzheimer's disease

Neurofibrillary tangles are a major neuropathological hallmark of AD and their regional distribution correlates with clinical symptoms. Initially, tangles develop in the transentorhinal cortex, an intermediary region between the perirhinal cortex and the entorhinal cortex (Braak and Braak, 1991). In light of the monkey data showing that damage to rhinal areas results in severe deficits on DNMS (Meunier et al., 1993; Chavoix et al., 2002) associated with brain changes reminiscent of those occurring in AD (Blaizot et al., 2002), we hypothesized that patients with early AD would show impaired visual recognition memory in a task modeled from the monkey DNMS task (detailed in Didic et al., 2011).

This is indeed what we showed using the DMS48, a test of visual recognition memory (Barbeau et al., 2004a). The DMS48 is based on the classic delayed matching-to-sample task used in non-human primates, in which monkeys have to choose between a target and a distractor during the recognition phase. In a preliminary study, all patients with mild and moderate probable AD were impaired on the DMS48. This result has been replicated, although interestingly with more variability, in a

[1] Egan JP. 1958. Recognition memory and the operating characteristic (Tech. Note AFCRC-TN-58–51). Bloomington: Indiana University, Hearing and Communication Laboratory.

recent article by Poissonnet et al. (2012). The DMS48 was also submitted to a group of subjects meeting the criteria for amnestic Mild Cognitive Impairment (aMCI), patients at high risk to evolve towards Alzheimer's dementia. Patients with aMCI were found to be impaired on the DMS48, their performance being intermediate between that of control subjects and patients with mild AD. However, a large dispersion was observed in this group: some patients scored below controls on the task (78% of the patients), whereas the others succeeded. These two subtypes of aMCI patients in fact suffer from different brain dysfunctions.

Hypoperfusion and grey matter loss predominate in the frontal lobes in aMCI patients performing normally on the DMS48, whereas they predominate in the temporo-parietal and medial temporal regions (rhinal areas included) in aMCI patients impaired on the DMS48 (Guedj et al., 2006; Barbeau et al., 2008). In addition, poor performance on DMS48 is associated with decreased NAA/mIno ratios, a marker of neuronal dysfunction or axonal injury, in the MTL (Didic et al., 2010). The patterns of hypoperfusion and grey matter loss observed in aMCI patients impaired on the DMS48 are very similar to what is usually observed in early AD (Ceccaldi and Cozzone, 2010). In addition, performance on the DMS48 correlated with the left perirhinal cortex in our VBM study, in line with the correlation that exists between recognition memory performance and rhinal areas in mild AD (Wolk et al., 2008). Taken together, these three neuroimaging studies bring strong arguments supporting the hypothesis that aMCI patients failing on the DMS48 display abnormalities of the MTL, and in particular of anterior subhippocampal structures (the perirhinal and entorhinal cortices). A clinical 6-year follow-up indicates that impaired performance on the DMS48 predicts conversion to AD with a sensitivity and specificity of 81.8% (Didic et al., 2010). These data imply that the subgroup of aMCI patients failing on the DMS48 should be considered at very high risk to further develop a dementia of the AD type.

Recognition memory is generally found to be impaired in AD before dementia sets in (Ivanoiu et al., 2005; Bennett et al., 2006; Westerberg et al., 2006; Perri et al., 2007; Anderson et al., 2008; Ally et al., 2009) and at least one study (Wolk et al., 2008) demonstrated an impairment in several familiarity tasks. Our studies on aMCI patients (reviewed in Didic et al., 2011) help characterize the memory impairment at the onset of this devastating disease. They support the idea that familiarity-based memory for single items is impaired very early in the course of the disease, thereby demonstrating that early AD memory deficits are not solely episodic (Barbeau et al., 2012). All in all, this line of research inspired by studies in the monkey shows how basic and applied research are directly linked.

10. Conclusion

The study of recognition memory has relied on a continual coming and going between research in the animal and in the human. After 50 years of research, two issues remain hotly debated: the division of labor between the different medial temporal structures, and how best to model the familiarity and recollection processes underlying recognition memory. The evidence reviewed here in monkeys and the two French patients, FRG and JMG, supports the modular view attributing familiarity to rhinal areas and recollection to the hippocampus rather than the alternative view of recognition memory as a unitary process equipotentially served by the hippocampus and subjacent cortex. Overall, the use of converging paradigms in both animals and humans as well as the study of recognition memory in degenerative diseases have brought considerable progress in our understanding of medial temporal functions, in particular by revealing the importance of cortical regions surrounding the hippocampus and the very early disruption of recognition memory in the course of AD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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