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Role of hippocampal CA1 atrophy in memory encoding deficits in amnestic Mild Cognitive Impairment

Marine Fouquet [a,b,c,d], Béatrice Desgranges [a,b,c,d], Renaud La Joie [a,b,c,d], Denis Rivière [e], Jean-François Mangin [e], Brigitte Landeau [a,b,c,d], Florence Mézenge [a,b,c,d], Alice Pélerin [a,b,c,d,f], Vincent de La Sayette [a,b,c,d,f], Fausto Viader [a,b,c,d,f], Jean-Claude Baron [g], Francis Eustache [a,b,c,d], Gaël Chételat [a,b,c,d,*]

[a] INSERM, U1077, Caen, France
[b] Université de Caen Basse-Normandie, UMR-S1077, Caen, France
[c] Ecole Pratique des Hautes Etudes, UMR-S1077, Caen, France
[d] Centre Hospitalier Universitaire, U1077, Caen, France
[e] CEA, Laboratoire de NeuroImagerie Assistée par Ordinateur, Neurospin, Gif-sur-Yvette, France
[f] Centre Hospitalier Universitaire, Service de Neurologie, Caen, France
[g] INSERM UMR 894, Sorbonne Paris Cité, Université Paris Descartes, France

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ABSTRACT

Identifying the specific substrates of memory deficits in early Alzheimer's disease would help to develop clinically-relevant therapies. The present study assesses the relationships between encoding versus retrieval deficits in patients with amnestic Mild Cognitive Impairment (aMCI) and atrophy specifically within the hippocampus and throughout the white matter. Twenty-two aMCI patients underwent T1-weighted MRI scans and neuropsychological testing. Grey matter and white matter segments obtained from the MRI images were each entered in correlation analyses, assessed only in the hippocampus for grey matter segments, with encoding and retrieval memory performances. For the grey matter segments, the resulting spmT correlation maps were then superimposed onto a 3D surface view of the hippocampus to identify the relative involvement of the different subfields, a method already used and validated elsewhere. Memory encoding deficits specifically correlated with CA1 subfield atrophy, while no relationship was found with white matter atrophy. In contrast, retrieval deficits were weakly related to hippocampal atrophy and did not involve a particular subfield, while they strongly correlated with loss of white matter, specifically in medial parietal and frontal areas. In aMCI patients, encoding impairment appears specifically related to atrophy of the CA1 hippocampal subfield, consistent with the predominance of encoding deficits and CA1 atrophy in aMCI. In contrast, episodic retrieval deficits seem to be underlain by more distributed tissue losses, consistent with a disruption of a hippocampo-parieto-frontal network.

Introduction

For the development of new therapeutic agents for Alzheimer's disease (AD), the identification of clinically relevant targets is essential. Along this line, it is important to further our knowledge of the brain structures specifically involved in episodic memory deficits that characterize the disease, especially at its pre-dementia stage, i.e. when neuropathological processes are still limited and cognitive deficits still partly reversible.

In patients with amnestic Mild Cognitive Impairment (aMCI), the clinical entity that best represents the pre-dementia stage of AD (Petersen, 2005), previous studies have consistently reported a relationship between episodic memory impairment and hippocampal atrophy (Convit et al., 1997; Fjell et al., 2008; Hanseeuw et al., 2011; Jhoo et al., 2010; Leube et al., 2008; Schmidt-Wilcke et al., 2009; Serra et al., 2010). However, episodic memory on the one hand involves several distinct processes, notably encoding and retrieval of the information, while, on the other hand, the hippocampus is a complex cytoarchitectonic structure made up of four Cornu Ammonis subregions (CA1, 2, 3 and 4, respectively), the dentate gyrus (DG) and the subiculum (Duvernoy, 1998). These hippocampal subfields differ in terms of their cellular nature and organization, as well as their connectivity with the rest of the brain (Amaral, 1993; Teyler and DiScenna, 1984). It is thus possible that these subfields have a

Abbreviations: AD, Alzheimer's disease; aMCI, amnestic Mild Cognitive Impairment; CA, Cornu Ammonis; DG, dentate gyrus; HIPER, HIppocampal Encoding/Retrieval Pattern; GM, grey matter; WM, white matter; SVC, small volume correction; 3D, three-dimensional; TGA, transient global amnesia; NFTs, neurofibrillary tangles; DTI, diffusion tensor imaging.

* Corresponding author at: Inserm, EPHE, Université de Caen Basse Normandie, Unité U923, Laboratoire de Neuropsychologie, GIP Cyceron, Bd H Becquerel, 14074 Caen cedex, France. Fax: +33 2 31 47 02 75.
E-mail address: chetelat@cyceron.fr (G. Chételat).

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differential role in episodic encoding and retrieval deficits in aMCI patients. In healthy subjects, the regional specialization of encoding and retrieval processes within the hippocampus has been the topic of intensive investigations. An antero-posterior gradient has been posited as part of the HIppocampal Encoding/Retrieval Pattern (HIPER) model (Lepage et al., 1998), and a specific role for the different hippocampal subfields has been more recently proposed (Eldridge et al., 2005), though there is no clear-cut evidence to date as regards the specific relationships between each hippocampal subfield and memory processes (see Carr et al., 2010a for review).

In aMCI patients, we previously reported that both encoding and retrieval deficits were related to hippocampal grey matter (GM) atrophy (Chételat et al., 2003). Nevertheless, in early AD, encoding deficits tend to predominate over retrieval deficits (Pike and Savage, 2008; Wang and Zhou, 2002; see Belleville et al., 2008 for review) while hippocampal atrophy preferentially affects the CA1 subfield (Apostolova et al., 2006a, 2006b; Apostolova et al., 2010b; Atienza et al., 2011; Becker et al., 2006; Chételat et al., 2008; Mueller et al., 2010; Wang et al., 2006; Yassa et al., 2010); even if atrophy of CA3/DG (Atienza et al., 2011; Yassa et al., 2010) and subiculum (Apostolova et al., 2010a) has also been reported in aMCI. Otherwise, previous studies have reported a specific link between neuronal loss in CA1 and episodic memory impairment in AD (Zarow et al., 2005) or atrophy in CA1 and episodic memory deficits in mild AD (Sarazin et al., 2010), but in these studies encoding was not distinguished from retrieval. Taken altogether, these results raise the hypothesis of a specific role for CA1 atrophy in the encoding deficits of aMCI.

With respect to retrieval deficits in aMCI, although also broadly related to hippocampal atrophy, they are thought to involve dysfunction within a wider network. For instance, a role for posterior cingulate hypometabolism has previously been suggested (Chételat et al., 2003). Moreover, when using free recall tasks, which mainly depend on retrieval capacities in contrast to recognition tasks, episodic memory impairment in AD has been related to damage at multiple sites of a functionally integrated network comprising medial temporal lobe and related limbic–diencephalic circuitry (namely, the posterior cingulate cortex, thalamus and mammillary bodies (Nestor et al., 2006)), as well as the anterior cingulate (Desgranges et al., 1998) and frontal cortex (Eustache et al., 2004; see Salmon et al., 2008 for review). Overall, therefore, retrieval deficits in aMCI patients are believed to result from disruption of this network and are thus expected to depend on integrity of the connectivity within this network, rather than on damage to a specific hippocampal subfield.

The present study aims to test these hypotheses regarding both encoding and retrieval deficits, by assessing the specific relationships between these deficits in aMCI patients and both hippocampal subfields GM atrophy and white matter (WM) atrophy across the brain as a reflection of structural connectivity integrity.

Materials and methods

Patients

The present sample of aMCI patients partly overlaps with that used in our previous publications using MRI data (Chételat et al., 2003, 2005, 2008; Villain et al., 2010), although only those patients in whom both MRI data and scores at the 'Encoding Storage Retrieval' (ESR; Eustache et al., 1998) memory task were available were included in the present study.

Briefly, twenty-two aMCI patients were recruited through a memory clinic, which they attended for a memory complaint. They were all right-handed, aged over 55 years and had at least 7 years of education (see Table 1 for their demographic and clinical data). They underwent medical, neurological, neuropsychological, and neuroradiological examinations, and were selected according to current criteria for aMCI, i.e. isolated episodic memory deficits (<1.5 SD of the normal mean matched for age and education), normal performance in other areas of cognition and in global cognition (assessed with the MMSE scale (Folstein et al., 1975)), and NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) not met (see Chételat et al., 2005 for details). According to the Declaration of Helsinki, each patient gave written informed consent to participate in the study, which was approved by the regional ethics committee.

Table 1
Demographic, clinical and neuropsychological data of aMCI patients included in the present study as compared to a group of matched healthy controls.

	aMCI patients	Healthy controls	
Number (women/men)	22 (12/10)	30 (18/12)	ns
Age (years; mean ± SD)	72.1 ± 8.7	68.2 ± 3.9	ns
Education (years; mean ± SD)	10.0 ± 3.3	9.7 ± 2.4	ns
MMSE (mean ± SD)	27.4 ± 1.4	–	–
Encoding (mean ± SD)	12.8 ± 1.7	14.8 ± 1.2	***
Retrieval (mean ± SD)	6.1 ± 2.4	7.5 ± 2.3	*

SD: standard deviation; ns: non-significant; * $p<0.05$; *** $p<0.001$.

Encoding and retrieval episodic memory capacities were evaluated using the ESR task already used in a previous study showing decreased performances in both processes in a partially overlapping sample of aMCI patients as compared to age-matched controls (see Chételat et al., 2003 for details on the task and Table 1 for their scores). Briefly, the ESR task includes two learning phases (one superficial and one deep) of two different lists. Each list comprised 16 words, belonging to 16 different semantic categories. For the first list, patients had to say whether the first and last letters of each orally presented word were in alphabetical order, without any instruction to memorize. At the end of this incidental superficial encoding phase, a recognition phase was carried out where patients had to recognize the 16 target words among distractors. Each target word was presented visually, one by one, with three distractors, one semantically linked, one phonetically linked, and the third with no link with the target word. For each of these 16 presentations, patients were systematically required to point to a word with their finger, the one they recognized, or otherwise the one they chose at random. For the second list, patients were asked to memorize the words. In order to induce a semantic processing, they had to generate orally a sentence that defined or described the orally presented word. Every two words, an immediate cued recall task was performed using a semantic category cue, in order to ensure that encoding was made and to reinforce its semantic nature. If the patient failed, he was reminded of the word, and again requested to make a sentence containing the target, and to recall it in response to its categorical cue. At the end of this 16-word intentional deep encoding, patients were asked to recall as many words as possible, in any order and without time limitation. Performance in recognition after incidental superficial encoding from the first list is assumed to mainly reflect encoding capacity, as recognition is supposed to compensate for potential retrieval deficits. In contrast, performance in free recall after intentional deep encoding is assumed to preferentially reflect retrieval capacity as encoding is supported, thereby compensating for potential deficits in spontaneous encoding capacities. Note that psychometric scores necessarily reflect both encoding and retrieval capacities, so that there is no measurement that would only reflect one of these two processes. The ESR task has been especially designed to place maximal demand on encoding and minimal demand on retrieval to assess encoding processes and conversely. Thus, although they are not pure measurements of each process, they will be designated in what follows by the process they preferentially tap, i.e. encoding and retrieval scores, for the sake of simplicity (Gabrieli et al., 1997).

MRI data acquisition and processing

Within a few days after inclusion, each patient underwent a 1.5 Tesla T1-weighted MRI volume scan, all on the same scanner