Item familiarity and controlled associative retrieval in Alzheimer's disease: An fMRI study.

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Abstract

Typical Alzheimer's disease (AD) is characterized by an impaired form of associative memory, recollection, that includes the controlled retrieval of associations. In contrast, familiarity-based memory for individual items may sometimes be preserved in the early stages of the disease. This is the first study that directly examines whole brain regional activity during one core aspect of the recollection function: associative controlled episodic retrieval (CER), contrasted to item familiarity in AD patients. Cerebral activity related to associative CER and item familiarity in AD patients and healthy controls (HC) was measured with functional magnetic resonance imaging during a word-pair recognition task to which the process dissociation procedure was applied. Some patients had null CER estimates (AD–), whereas others did show some CER abilities (AD+), although significantly less than HC. In contrast, familiarity estimates were equivalent in the three groups. In AD+, as in controls, associative CER activated the inferior precuneus/posterior cingulate cortex (PCC). When performing group comparisons, no region was found to be significantly more activated during CER in HC than AD+ and vice versa. However, during associative CER, functional connectivity between this region and the hippocampus, the inferior parietal and dorsolateral prefrontal cortex (DLPFC) was significantly higher in HC than in AD+. In all three groups, item familiarity was related to activation along the intraparietal sulcus (IPS). In conclusion, whereas the preserved automatic detection of an old item (without retrieval of accurate word association) is related to parietal activation centred on the IPS, the inferior precuneus/PCC supports associative CER ability in AD patients, as in HC. However, AD patients have deficient functional connectivity during associative CER, suggesting that the residual recollection function in these patients might be impoverished by the lack of some recollection-related aspects such as autonoetic quality, episodic details and verification.

I. Introduction

Long-term memory impairment, as evidenced by impaired recall and recognition memory performance, is one hallmark of Alzheimer's disease (AD). According to the dual-process models of memory, two independent functions support recognition memory performance: recollection and familiarity. Recollection reflects the controlled, conscious retrieval of information, including the recovery of details from the encoding context. Familiarity reflects a relatively automatic process of global assessment of memory strength or stimulus recency without controlled access to the associated contextual information (for reviews, see Yonelinas, 2002, and Yonelinas et al., 2010). In the same vein, within recognition memory assessment, item recognition can be distinguished from associative recognition. Associative recognition usually engages the ability to retrieve the relationship between individual items or between items and their context. Since recollection involves the retrieval of specific qualitative information about the event, it is generally assumed that associative memory performance depends mainly on the recollection function (although there are some exceptions, see below). On the contrary, it is often assumed that performance on item recognition tasks relies mostly on familiarity in the absence of recollection (e.g. Montaldi and Mayes, 2010; Yonelinas, 2002; Yonelinas et al., 2010). A few studies on long-term memory in AD have assessed memory for items and associations as well as the familiarity and recollection functions.

Studies focusing on the distinction between recollection and familiarity have mainly used process-estimation methods, such as the process dissociation procedure and the Remember/Know (R/K) procedure. The process dissociation procedure (PDP) allows one to meticulously assess controlled and automatic processes within a single memory task (Jacoby,

1991; Jacoby et al., 1993). This procedure focuses on the controlled episodic retrieval (CER) aspect of the recollection function. The term "controlled" in this framework should not be considered in an absolute sense. It refers to a goal-driven process involving conscious and analytic access to memories that counteracts a response driven by automatic memory influences. With this method, some studies have found that CER is severely impaired while automatic processes are relatively preserved or, at least, less impaired than CER (Adam et al., 2005; Knight, 1998; Smith and Knight, 2002). Analogous results have also been found in patients likely to be at a pre-dementia stage of AD such as patients with amnesic Mild Cognitive Impairment (aMCI) and in patients with questionable AD (Anderson et al., 2008; Bastin et al., 2010; Tse et al., 2010). Another process estimation method, the Receiver Operating Characteristics curves analysis (ROCs; for a review, see Yonelinas and Parks, 2007), has been used in patients with MCI to assess recollection and familiarity. Like studies that used the PDP, Ally et al.'s (2009a) and Embree et al.'s (2012) experiments with the ROCs procedure showed that recollection was severely impaired. Interestingly, Ally et al. found that familiarity estimates were reduced for studied words in patients with MCI, while Embree et al. showed that familiarity estimates were reduced for studied words but not for studied pictures in MCI. Similar findings have been obtained by using event-related potential (ERP) measurements during a recognition task in patients with MCI by Ally et al. (2009b). These authors showed that ERP components typically associated with familiarity were diminished for studied words but not for studied pictures in patients with MCI.

The recollection and familiarity functions can also be evaluated with the Remember/Know procedure (Gardiner, 1988; Tulving, 1985). This procedure distinguishes recollection from familiarity on the basis of phenomenal experience or level of consciousness. More concretely, participants are asked to report whether they recognise items through recollection of episodic

details of the encoding context (Remember) or through a feeling of familiarity without any recollective experience (Know). Most of the studies that assessed the subjective aspects of recollection and familiarity in AD patients by using the Remember-Know procedure found that the experience of remembering, but not familiarity, was significantly impaired in AD patients (Dalla Barba, 1997; Piolino et al., 2003; Rauchs et al., 2007). However, a more recent study has found that both Remember and Know responses were reduced in AD patients (Hudon et al., 2009). In contrast, to date, all the studies that have assessed phenomenal aspects of recollection and familiarity in patients with Mild Cognitive Impairment have found that the recollective experience was reduced but not the feeling of familiarity (Belleville et al., 2011; Hudon et al., 2009; Serra et al., 2010). Finally, recollection and familiarity have been more indirectly assessed by means of experimental manipulations (e.g. test format: Westerberg et al., 2006; salience of fluency: Algarabel et al., 2009). Whereas Westerberg et al. found that recollection was severely impaired and familiarity relatively preserved in MCI patients, Algarabel et al. (2009) suggested that familiarity could be impaired in MCI patients. In summary, there is no consensus regarding the preservation of familiarity in patients with MCI and AD, but all studies agree that recollection is severely impaired in both patient populations.

In the same vein, Irish et al. have recently examined the quality of the recollective experience for retrograde memories in AD patients (Irish et al., 2011a, 2011b). They reported that AD patients were impaired across a range of behavioural markers inherent in the recollective experience such as self-referential imagery, vividness and retrieval of contextual details. Self-reference and vividness are two main aspects of autonoesis, that characterized episodic retrieval. According to Tulving (2002), the term autonoetic has been used to refer to this special kind of consciousness that allows us to be aware of subjective time in which events

happened. Autonoetic awareness (or autonoesis) is required for remembering, to re-experience, through autonoetic awareness, one's own previous experiences (Tulving, 2002). Accordingly, Irish et al. concluded that AD patients have impoverished autonoetic consciousness. The authors found an analogous profile of impairment for MCI patients' recollective experience (Irish et al., 2010). These findings highlight the complex nature of the recollective experience and suggest that, even when AD patients are able to experience subjective recollection, this process may be qualitatively different from the recollection process in healthy ageing. In particular, AD patients often fail to consciously retrieve details associated with the target memory. Similarly, Tendolkar et al. (1999) have found that AD patients who had smaller hippocampi showed an inability to recollect the study context in a verbal recognition memory task.

A few studies have investigated long-term memory for associations in AD patients. Studies that have used the Paired Associate Learning Task (PAL) from the Cambridge Neuropsychological Testing Automated Battery (CANTAB; Cambridge Cognition Place, UK) suggest that patients with AD (Lee et al., 2003) and patients with MCI (de Rover et al., 2011) have deficits in associative memory. Furthermore, Fowler et al. (2002) found that performance on the PAL was impaired in early-stage AD patients, even before standard neuropsychological measures detected any deterioration. Along the same lines, Pariente et al. (2005) found that AD patients' performance was reduced in a face-name association task. One study directly investigated item and associative recognition in AD patients (Hanaki et al., 2011). The authors found that both item and associative recognition memory were impaired in AD patients. Other authors derived item and associative memory scores from standardised tests of recall in patients with MCI (Troyer et al., 2008). They found that both item and associative recall were impaired in MCI patients, but that associative recall was

more impaired and more sensitive to MCI than item recall. Interestingly, it appeared that AD patients' difficulties with associations are not specific to long-term memory but are also robustly demonstrated in short-term memory (Della Sala et al., 2012; Parra et al., 2009, 2010a, 2010b; van Geldorp et al., 2012).

Finally, some studies have used an associative recognition task to disentangle recollection- versus familiarity-based memory performance. In most of these studies, participants studied word pairs and were then asked to distinguish between intact pairs and recombined pairs during a recognition test. In this way, Gallo et al. (2004) showed that AD patients had difficulties engaging controlled recall of an originally studied pair of words in order to reject a rearranged version of the pair. These authors interpreted the impaired recall-to-reject process as evidence of altered recollection-based monitoring in AD patients. Similarly, Algarabel et al. (2012) used the proportion of hits for intact pairs minus the proportion of false alarms for recombined pairs as an index of recollection in AD patients and patients with MCI. They found that recollection scores were deficient in these patients. Wolk et al. (2008, 2011) applied the PDP to an analogous word pair recognition task. They found that both recollection and familiarity scores were deficient in patients with MCI and AD.

In summary, impaired recollection and associative memory are two robust characteristics of the memory profile in AD. These alterations may be observed even at very early stages of AD, when the criteria for dementia have not yet been met. Recollection is a complex function that engages many processes. Studies that have examined the controlled aspect of recollection in AD patients suggest that this process is impaired, whereas the impairment of automatic memory processes is subject to debate. Studies that have examined the subjective experience accompanying recollection suggest that subjective remembering is impaired, whereas

whether the experience of knowing is preserved or impaired is less clear. Furthermore, studies that have investigated the quality of the recollective experience in AD patients suggest that it lacks contextual details and autonoesis. These results are similar to those of the studies of associative memory in AD patients that suggest that memory for associations, whether short- or long-term, is altered in these patients. Together, then, these findings suggest that the controlled retrieval of associations in long-term memory in AD patients should be severely deficient. In addition, one might expect the subjective experience of remembering that accompanies this retrieval to be impaired in AD.

Several theories have been proposed to model how associations in long-term memory are supported by the medial temporal lobe (MTL) and therefore are associated with recollection and familiarity. According to Yonelinas (2002; Yonelinas et al., 2010), retrieval of inter-item associations is mainly supported by recollection. However, the authors noted one exception: if the two items have been encoded as a whole item in the study phase (i.e. unitisation)[1], familiarity may contribute to associative memory judgements. Since the hippocampus is critical for recollection but plays no role in familiarity-based recognition, one might expect that recognition of non-unitised associations should be related to the hippocampus whereas item recognition which does not engage associative retrieval should be supported by extra-hippocampal medial temporal regions (Yonelinas et al., 2010). According to the Domain-Dichotomy (DD) view (Mayes et al., 2007), unitised associations and within-domain associations, which are associations between identical or very similar kinds of items (e.g. face-face pair), might be supported by familiarity via the perirhinal cortex. In contrast, between-domain associations, which are associations between different kinds of items (e.g. face-name pair), are mainly supported by the hippocampus via recollection. However, to account for divergent findings in the literature, the authors suggested that recognition of

within-domain associations, such as word pairs, is supported by the recollection function if the items have been linked at encoding by using a mediator (e.g. a sentence or a mental image). A few years later, the authors proposed a modified version of the DD view, called the Convergence, Recollection and Familiarity Theory (CRAFT; Montaldi and Mayes, 2010) in which they added a role for the parahippocampal cortex in context recognition via familiarity. A very close perspective, the Binding of Item and Context model (BIC), was proposed by Diana et al. (2007; for a review of evidence in favour of this model, see also Ranganath, 2010). Like previous models, the BIC model proposes that the perirhinal cortex is involved in item familiarity-based recognition of items whereas the hippocampus is necessary to link one item to another or to the study context, so that the hippocampus plays a crucial role in the recollection of inter-item associations. Also similarly to previous models, the BIC model predicts that the perirhinal cortex might support associative recognition on the basis of familiarity if the items are encoded as a single unit (i.e. unitised). In addition, the BIC model suggests that the parahippocampal cortex is engaged during recollection of contextual information. In summary, current theories of the implementation of associative memory in the MTL diverge on some points, but convergence can be found in several respects. First, there is agreement that the hippocampus supports the retrieval of inter-item associations via recollection in many conditions. Second, all models suggest that the perirhinal cortex may be engaged in familiarity-based retrieval of associated items if these items were encoded as a single entity. Along these lines, recent findings obtained with various procedures suggest that familiarity, supported by the perirhinal cortex, may support recognition of the source associated with a given item when that source is encoded as a feature of the item (Diana et al., 2008, 2010, 2011).

Previous findings highlight the fact that most studies that have examined the brain regions associated with recollection and familiarity have focused on the MTL, mainly because recollection and familiarity were considered in the framework of associative memory versus item memory. Reviews of these studies suggest that generally, within the MTL, recollection seems to be associated with the hippocampus and the parahippocampal cortex whereas familiarity seems to be related to the perirhinal cortex (Diana et al., 2007; Eichenbaum et al., 2007). Regarding the fMRI data suggesting that the perirhinal cortex supports familiarity, it is noteworthy that, whereas subsequent familiarity is associated with activation in the perirhinal cortex during encoding (Davachi et al., 2003; Ranganath et al., 2004b), familiarity/item memory at retrieval has been found to be associated with deactivation in this region (Gonsalves et al., 2005; Henson et al., 2005; Weis et al., 2004).

However, Skinner and Fernandes (2007) suggested that, in fMRI studies of recollection and familiarity, the involvement of the MTL in relation to these processes depends on the specific demands of the tasks and the type of information involved. In the same vein, in a meta-analysis of fMRI studies examining episodic retrieval, Spaniol et al. (2009) showed that objective (source memory) and subjective ('remember' reports) recollection processes share brain activations, but that some regions were specifically involved in either objective or subjective recollection. In particular, the hippocampus was active for subjective but not objective recollection. In a recent study, Slotnick (2010) showed that, during memory retrieval, the inferior parietal cortex supports subjective remembering whereas the hippocampus mediates binding of item-related information. These findings highlight the fact that familiarity and recollection are supported by many different regions and that recollection is a high-level function characterised by multiple processes and consequently is related to different brain regions depending on the specific aspect targeted by the task. However, some

constants can be found in the patterns of brain activation related to recollection and familiarity functions, as already reported for the MTL. Within the parietal lobe, familiarity processes are preferentially associated with the superior parietal cortex whereas recollection processes are preferentially associated with the inferior parietal cortex (Kim, 2010; Skinner and Fernandes, 2007). Recollection processes are also preferentially associated with medial prefrontal and posterior cingulate cortex/precuneus activation (Kim, 2010). In a recent meta-analysis, Kim (in press) has shown that the inferior portion of the posterior precuneus was more associated with high-confidence Remember responses than with low-confidence Know responses, whereas superior portions of the precuneus show the reverse pattern. Therefore, one can assume that the posterior cingulate cortex and the inferior part of the precuneus form a whole entity involved in the recollection network.

Little is known about the brain substrates of the recollection/associative memory and familiarity/item memory processes in AD patients. Regarding associative memory, it has been found that patients with MCI and AD have altered hippocampal activation when compared to healthy controls during face-name recognition tasks (Pariente et al., 2005; Petrella et al., 2006). Furthermore, it has been found that patients with aMCI have impaired dynamic signal attenuation related to associative learning in the hippocampal region compared to healthy controls (Johnson et al., 2008). Interestingly, it has also been found that patients with MCI had impaired hippocampal activation when compared to healthy controls in an adaptation of the PAL task but only in the higher memory load condition (de Rover et al., 2011). Wolk et al. (2011) examined the relationships between the volume of MTL structures (hippocampus and extrahippocampal MTL) and the recollection/familiarity estimates derived with PDP from the word pair recognition task in AD, MCI and healthy older participants. They found that recollection performance was more related to

hippocampal volume than to extrahippocampal volume whereas familiarity performance was more associated with extrahippocampal volume than with hippocampal volume. However, no study has yet investigated how specific aspects of recollection and familiarity are related to brain functioning outside the MTL in AD patients. Bastin et al. (2010) performed cognitive-metabolic correlations between controlled memory performance and brain metabolism in questionable AD patients who were known either to remain stable or to meet the criteria for AD after 36 months. They found that CER was preferentially correlated with activity in the medial prefrontal cortex and the posterior cingulate cortex in questionable AD patients who subsequently received a diagnosis of Alzheimer's dementia. This study was a first attempt to identify brain regions related to the controlled aspect of recollection in the very early stages of AD. However, several questions remain unanswered. First, the brain regions supporting familiarity for individual items in AD patients are unknown. Second, whole brain regions associated with the recollection function, in particular CER, in demented patients are not well defined.

The main objective of this study was thus to measure brain activation during the CER aspect of recollection and during item familiarity in AD patients and healthy older participants, using fMRI. An objective recollection procedure focusing on the controlled retrieval process was preferred to a subjective memory procedure for two reasons. First, the R/K procedure measures recollection and familiarity on the basis of subjective reports, which can be inaccurate in some participants, particularly in those who have impaired cognitive abilities (Baddeley et al., 2001; Yonelinas, 2002). As the task was performed in the scanner, the accuracy of patients' choices could not be assessed. In the same vein, assessment of the qualitative aspects of the recollective experience, such as quality of reliving, amount of contextual details retrieved, quality of imagery and self-involvement, should preferentially be

performed using fine-grained scales, which is not easy to do in a scanner with demented patients. Since current theories and previous work suggest that retrieval of associations is a core process of the recollection function and that this process is impaired in AD patients, we applied the logic of the PDP to a word-pair recognition task in order to disentangle the recollection and familiarity functions during memory retrieval, as previously done in some behavioural studies (Wolk et al. 2008, 2011). After incidental encoding of unrelated word pairs, participants saw intact, recombined and new pairs. They were asked to make an old/new judgement on each pair. Participants were explicitly instructed to answer 'old' only if they had seen both words associated in the same pair during the encoding session, that is, only in case of an intact pair. The recombined pairs provided a condition in which controlled retrieval of the association was opposed to item familiarity (i.e. an exclusion condition). As the participants had seen both words previously, they were familiar with these items and thus, in the absence of controlled retrieval of the original association, they might be driven to incorrectly endorse the pair as an old one. In contrast, the intact pairs provided a condition in which controlled retrieval was congruent with familiarity. Thus, our task allowed associative CER to be disentangled from item familiarity in recognition performance. It targeted the controlled and associative aspects of episodic retrieval, but it did not exclude other aspects of the recollective experience (i.e. imagery, autonoesis and retrieval of contextual details such as thoughts are likely to be associated with the controlled retrieval process).

We examined brain regions specifically activated during item familiarity and during CER of associations. It is likely that some regions, such as the posterior cingulate cortex and the medial prefrontal cortex, mainly support the controlled aspect of the recollection function and therefore might be significantly activated specifically during CER. Other regions may be significantly activated in our healthy population sample during CER since they play a role in

the recollection function, such as the inferior parietal cortex, which is said to support the subjective experience of remembering (Slotnick, 2010). The design of our task does not allow an examination of how the retrieval of the associations is personally experienced by the participants and which region supports this process, since our task was designed to disentangle controlled retrieval of a pair from item familiarity. Intuitively, we can assume that healthy participants should feel that they have personally seen the association and, on the basis of current opinion regarding this process, one may assume this to be related to the inferior parietal cortex (Simons et al., 2010). According to the wide range of studies and reviews showing that the hippocampus plays a crucial role in retrieval of associated details, we should expect it to be involved in the recollection function. If these regions are related to recollection, they may be functionally connected to the regions supporting associative CER during recollection. To account for these assumptions, functional connectivity analyses were performed during recollection.

At the behavioural level, we expected that associative CER would be impaired in AD patients. We also expected that item familiarity might be impaired since some studies have found it to be already altered at the MCI stage. Regarding the brain substrates of familiarity, we expected, at least in control participants, signal changes in brain regions such as the superior parietal cortex, the intraparietal sulcus and the perirhinal cortex (Diana et al., 2007; Eichenbaum et al., 2007; Wagner et al., 2005). Regarding the recollection function, little is known about the specific role of different brain regions in the different processes. First, the brain regions that specifically mediate effortful and controlled retrieval have not yet been identified. Most studies that have examined controlled processes in episodic retrieval have focused on post-retrieval monitoring (e.g. Henson et al., 1999b). One study used an exclusion task in an fMRI scanner and suggested that this task engaged the DLPFC via post-retrieval

monitoring. However, although the engagement of this region was greater for the exclusion task, it was not specific to this condition (Rugg et al., 2003). To our knowledge, Bastin et al.'s (2010) study is the only published work which has investigated brain regions related to controlled memory retrieval by using exclusion and inclusion conditions thanks to the PDP. According to that study and congruently with the findings of previous fMRI studies of episodic memory, CER is likely to be related to activations in the medial prefrontal cortex and the posterior cingulate gyrus (Bastin et al., 2010; Kim, 2010) in healthy participants. In addition, one might expect that concomitant subjective remembering and retrieval of item-related information will be related to engagement of the inferior parietal cortex and the hippocampus, respectively, in healthy older participants (Slotnick, 2010). Finally, we hypothesised that associative CER would be related to greater engagement of these regions in the healthy participants than the AD patients since recollection abilities are known to be reduced in AD patients.

It is plausible that AD patients and healthy older participants will share brain activations in some regions, allowing for residual CER in AD patients. Moreover, one can hypothesise that, even when AD patients show some CER abilities, their experience may be impoverished, due to lower activations in brain regions supporting other aspects of the recollective experience such as autonoesis and retrieval of contextual details.

II. Methods

Participants

Seventeen healthy older adults (HC) and 32 patients diagnosed with mild probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria

(McKhann et al., 1984) participated in this study. Patients were recruited in the Memory Clinic of the University Hospital in Liège. The diagnosis was based on a clinical interview with the patient and a caregiver, and on neurological and neuropsychological examinations. Patients had FDG-PET as a biomarker, and it was consistent with the AD diagnosis (McKhann et al., 2011). HC were recruited from seniors' organisations in Liège and were paid for their participation. Ethical approval was obtained from the ethics committee of the University Hospital of Liège and each participant (and a close relative for probable AD patients) gave informed consent to participate in the study in accordance with the Declaration of Helsinki. Participants did not have MRI contraindications and they were able to read capital letters 2 cm high at a distance of 50 cm without spectacles. HC had no history of neuropsychiatric problems or memory difficulty. Participants who showed mild signs of brain leukoaraiosis on structural MRI, compatible with normal aging, were not excluded. Six AD patients were excluded: one because of artefacts in functional images, one because of movements in the scanner, two had more than 35% of non-responses, one pressed the same button for 97% of the test items and one confused the two response buttons. In the samples included, 15 patients were taking an acetylcholinesterase inhibitor, 8 patients were taking ginkgo biloba and 4 patients had no drug treatment for AD symptoms. Gender was similarly distributed among HC (F: 6, 35%; M: 11, 65%) and probable AD groups (F: 11, 42%; M: 15, 58%; $\chi^2 = .21$; $p = .65$). The groups did not differ significantly with regard to years of formal education [$t(40) = –.6.1$; $p = .54$], with 13.0 (SD: 2.9) years of education on average in the HC group and 12.4 years (SD: 3.7) in the probable AD patient group. HC were on average younger (68.6 ± 5.0) than probable AD patients (75.6 ± 7.1; $t(41) = 6.1$; $p = .005$); therefore age was taken as a confounding covariate in subsequent analyses. All patients and HC were assessed with the Dementia Rating Scale (Mattis, 1973) after the fMRI session and

performance was significantly lower in the probable AD patients (124.3 ± 9.4) than in the HC (139.1 ± 2.9; $T(41) = -6.3$; $p < .001$).

Materials

A set of 314 words were selected from the MRC Psycholinguistic database and translated into French. Word length ranged from 4 to 8 letters (M = 5.8; SD: 1.2), and the words had an average frequency of 72 occurrences per million (SD: 128; Francis and Kucera norms, 1982). On scales of 100–700, the words had an average imagery rating of 578 (SD: 40), an average concreteness of 578 (SD: 42) and an average familiarity of 545 (SD: 46). Ten young and 10 older volunteers were asked to assess the emotional valence of these words on a scale ranging from 1 (very positive) to 10 (very negative). Emotional valence ranged from 2.5 to 7.5 (M: 4.6; SD: 1). The words were randomly divided into 157 word pairs. The words within each pair had no obvious semantic relationship to each other. Three pairs were used as study practice trials and four other pairs were used as test practice trials. An 'intact' and 'recombined' version of each pair was created: the recombined pairs were formed by switching words from two pairs (see experimental paradigm in Figure 1). Sixty baseline pairs formed by two series of 6 x's were also created. These pairs serve as baseline events in which memory and semantic process of the words are not supposed to be engaged. Thirty baseline pairs were pseudo-randomly interspersed between study trials and 30 baseline pairs were pseudo-randomly interspersed between recognition trials.

Procedure

The study phase was performed in the scanner to allow participants to get used to the fMRI environment and to match encoding and retrieval environments. One hundred and three word pairs were presented in random order. In each pair, the words appeared one above the other in

a white font on a black background using Cogent software running on MATLAB 6.1. (Mathworks Inc., Sherborn, MA). Participants were instructed to form a mental image in which the referents of both words interacted, to decide which was larger in size and to press the button corresponding to the position of the largest item on the screen (up or down). Participants were given an example: for the pair 'hospital lion', one could imagine a lion going to the hospital with a broken leg; the biggest referent is the hospital. Encoding was incidental as participants were not informed that there would be a subsequent memory test. The study phase was self-paced and each pair was followed by a 500 msec fixation cross. Participants performed the encoding task twice. There was a 30 sec break at the end of the first administration of the task during which participants stayed in the scanner.

Immediately after the study phase, instructions for the recognition task were given to the participants and brief practice trials (with debriefing) were performed outside the scanner. Then, the recognition task was performed in the scanner. In this task, participants saw three types of word pairs: 50 intact pairs, 50 recombined pairs and 50 novel pairs, as well as 30 baseline pairs. Baseline events were introduced to the participants as rest periods in which they did not have to answer. There were three counterbalanced lists such that each test pair served as an intact, recombined, or novel pair. Test pairs were presented in the same manner as at study. Pair presentation was pseudo-randomised with the restriction of a maximum of three sequential pairs of the same type. Participants were asked to indicate whether the word pair was 'old' or 'new' by pressing, respectively, the left or the right button within 8 sec. The end of the 8 sec limit or the keypress initiated the presentation of the next pair. Participants were told to answer 'old' only if the word pair was exactly the same as one presented in the study task. Therefore correct responses are 'old' for intact pairs and 'new' for recombined and new pairs. The recognition task was followed by a debriefing with the participant. Care

was taken to ensure that each participant understood these instructions during the practice trials and the debriefing. Examples of study and test trials are reported in Figure 1.

Behavioural Analysis

Following the principles of the PDP (Jacoby, 1991; Jacoby et al., 1993), intact pairs represent the inclusion condition because item familiarity and associative CER lead to the same answer (‘old’) whereas recombined pairs represent the exclusion condition because item familiarity and CER of the pair lead to different answers (‘old’ and ‘new’, respectively). The contribution of pairs’ CER and item familiarity processes can be assessed on the basis of the participants’ performance in the two conditions. In the inclusion condition (I), participants were able to correctly label the intact pair as ‘old’ because they retrieved the association they formed during the study phase (R) or because they had a feeling of familiarity for both items of the pair (F) without any CER. Thus, the probability of labelling an intact pair as ‘old’ in the inclusion condition is formalised as $I = R + F * (1–R)$. By contrast, in the exclusion condition (E), participants might incorrectly label a recombined pair as ‘old’ (false alarm) because both words of the pair felt familiar although participants did not recollect the association they had formed in the study phase. So, the probability of responding ‘old’ to a recombined pair in the exclusion condition is represented by $E = F * (1–R)$. The proportion of CER contributing to task performance can then be estimated by subtracting the proportion of false alarms to recombined pairs from the proportion of correct recognitions of intact pairs: $CER = R = I–E$. The proportion of familiarity engaged during the task can be obtained by dividing the proportion of false alarms to recombined pairs by the estimated proportion of a failure of CER: $F = E / (1–R)$.

Data Acquisition

Functional data were acquired on a 3 Tesla scanner (Siemens, Allegra, Erlangen, Germany) using a T2* sensitive gradient echo EPI sequence (TR = 2130 msec, TE = 40 msec, FA 90°, matrix size 64 X 64 X 32, voxel size 3.4 X 3.4 X 3.4 mm^3). Thirty-two 3-mm thick transverse slices (FOV 22 X 22 cm^2) were acquired, with a distance factor of 30%, covering the whole brain. The first three volumes were discarded to account for T1 saturation. A structural MR scan was obtained at the end of the functional sessions (T1-weighted 3D MP-RAGE sequence, TR = 1960 msec, TE = 4.4 msec, FoV = 230 x 173 mm^2, matrix size 256 X 256 X 176, voxel size 0.9 X 0.9 X 0.9 mm). Head movement was minimised by restraining the subject's head using a vacuum cushion. Stimuli were displayed on a screen positioned at the rear of the scanner, which the subject could comfortably see through a mirror mounted on the standard head coil.

Data Processing and Statistical Analyses

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, http//www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks Inc., Sherborn, MA). Within each session, functional scans were realigned using rigid body transformations, iteratively optimised to minimise the residual sum of squares between the first and each subsequent image separately. The different sessions were further realigned together and a mean realigned functional image was then calculated by averaging all the realigned functional scans. The structural T1-image was coregistered to this mean functional image using a rigid body transformation optimised to maximise the normalised mutual information between the two images. The mapping from subject to MNI space was estimated from the structural image with the 'unified segmentation' approach (Ashburner and Friston, 2005). The warping parameters were then separately applied to the functional and structural images to produce normalised images of resolution 2 x 2 x 2 mm^3 and 1 x 1 x 1 mm^3

respectively. Finally, the warped functional images were spatially smoothed with a Gaussian kernel of 8 mm full-width at half maximum (FWHM).

For each participant, BOLD responses were modelled at each voxel, using a general linear model. Analyses focused on the recognition phase. Eight regressors were defined to cover the two types of responses for the three types of pairs (correct responses to an intact pair, incorrect responses to an intact pair, correct responses to a recombined pair, incorrect responses to a recombined pair, correct responses to a novel pair and incorrect responses to a novel pair), baseline events and non-responses. The design matrix also included the realignment parameters to account for any residual movement-related effect. Regressors were convolved with the canonical HRF. A high pass filter was implemented using a cut-off period of 128 sec in order to remove the low-frequency drifts from the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order 1 (+ white noise). For each participant, after estimating the parameters of the model, five linear contrasts were calculated. Activity associated with associative CER was identified by contrasting correct recognition of intact pairs (Hit_IP, that is 'old' responses to intact pairs) versus false alarms for recombined pairs (FA_RP, that is 'old' responses to recombined pairs). Indeed, since Hit_IP involves both pair CER and item familiarity whereas FA_RP involves only item familiarity, brain activation related to pair CER can be isolated by subtracting brain activations related to FA_RP from brain activation related to Hit_IP. Since HIT_IP and FA_RP shared familiarity for individual items, brain activation related to item familiarity was identified by estimating the mean effect of brain activation related to Hit_IP and brain activation related to FA_RP. This analysis aimed to examine brain activations which are common to both Hit_IP and FA_RP. Since familiarity may also be related to MTL deactivation, brain deactivation related to item familiarity was

also identified by the mean effect of brain deactivation related to Hit_IP and brain deactivation related to FA_RP. For the sake of completeness, familiarity for individual items was also examined by contrasting correct recognition of intact pairs (Hit_IP, that is, 'old' responses to intact pairs) versus correct rejection of recombined pairs (CR_RP, that is, accurate 'new' responses to recombined pairs). This contrast was based on the assumption that Hit_IP involves both CER and familiarity whereas CR_RP is driven by controlled retrieval of the correct association (i.e. a *recall-to-reject* process) therefore brain activation related to item familiarity can be isolated by subtracting brain activations related to CR_RP from brain activation related to Hit_IP. However, this contrast is not as pure as the mean effect of Hit_IP and FA_RP. Indeed, a 'new' answer to a recombined item (CR_RP) may also be driven by the absence of familiarity/recollection for the items of the pair, and therefore subtracting brain activations related to CR_RP from brain activations related to Hit_IP may isolate both familiarity and CER.

First-level analyses of individual participants' data were conducted using a fixed-effect approach. The corresponding contrast images were smoothed (6-mm FWHM Gaussian kernel) in order to reduce the remaining noise due to inter-subject differences in anatomical variability in the individual contrast images. They were then entered in a second-level analysis, corresponding to a random-effect model. Because AD and HC groups were significantly different with regard to age (see above), this parameter was introduced as covariate at this level.

Based on the estimated proportion of CER, AD patients were divided into two groups. The patients who had an estimated proportion of CER superior to 0 were assumed to have engaged residual CER processes during the task (AD+) whereas AD patients who had an

estimated proportion of CER equal or inferior to 0 were assumed not to have done so (AD–). The random-effect matrix for item familiarity contrasts included the two groups of AD patients and the control group. To examine brain regions related to item familiarity processes that were commonly activated/deactivated by all three groups, a conjunction analysis was performed. This conjunction analysis for item familiarity had one strong advantage: since AD– patients are considered to have no residual CER abilities, the inclusion of this group in a conjunction analysis ensured that only brain regions that are related to the item familiarity function, and not to the CER process, were revealed. To rule out activations/deactivations related to visual, attentional and motor processes engaged during the display of the pairs in the mean effect of Hit_IP and FA_RP, the group conjunction analysis was performed on this mean effect with an exclusive masking (p-value of masking set at $p < .05$ uncorrected) of the conjunction of brain activations/deactivations related to correct rejection of novel pairs in the three groups. The main effect of correct rejection of novel pairs was chosen as the masking contrast since these events involve low-level processing of word pairs but no actual memory. For the CER contrast, the AD– patient group could not be included; thus, the random-effect matrix comprised the AD+ and control groups. A conjunction analysis between the two groups was performed to reveal brain regions activated by both the patients and the control participants during CER of association. The direct comparisons between the HC and AD+ groups were also performed to examine the brain activations that differ in the two groups.

Functional connectivity during associative CER was subsequently assessed by psychophysiological interactions (PPI). PPI analyses examine how activity in a particular brain region modulates activity in another brain region, specifically during one particular condition in contrast to another. Brain activity in individual CER maps was extracted in a sphere with a 10 mm radius centred on the most significant voxels in the brain region

revealed by the previous event-related random-effect analysis (physiological variable). CER (correct recognition of intact pairs versus false alarms to recombined pairs) represented the psychological variable. Next a new linear model was estimated for PPI analyses. Three regressors were constructed (plus the realignment parameters as covariates of no interest, as in the initial model). One regressor represented the psychological variable (CER). The second was the activity in the reference area. The third represented the interaction of interest between the first (psychological) and second (physiological) regressors. Significant contrasts for this psychophysiological regressor indicated a change in the regression coefficient between any observed brain area and the reference region, as a function of the memory process (CER). After smoothing (6-mm FWHM Gaussian kernel), these contrast images were entered in a second-level (random effects) analysis to perform inter-group comparisons (HC > AD+) in order to examine subtle aspects of whole brain functioning which are impaired in AD+ patients specifically during recollection.

The threshold for significant activation in whole-brain analysis was set at $p < .05$ FWE-corrected for multiple comparisons. Moreover, we had three regions of interest (ROI) defined a priori from the literature on episodic retrieval (Kim, 2010; Skinner and Fernandes, 2007; Spaniol et al., 2009) by an anatomical mask: the hippocampus, the posterior cingulate cortex/precuneus (PCC) and the medial prefrontal cortex (MPFC; this region of interest tentatively overlaps with BA8, BA9, BA10 and BA 32, which refer to the dorsomedial prefrontal and anterior cingulate cortex). These bilateral masks were extracted from the automatic anatomic labelling (AAL) of the MNI brain (Tzourio-Mazoyer et al., 2002) and used for small volume correction (SVC) of the p-values within each ROI. The statistical threshold was set at p corrected $\leq .05$ with a cluster minimum size $k = 10$.

III. Results

Behavioural Results

As mentioned above, AD patients were divided into two groups as a function of the estimated proportion of CER: AD patients who engaged residual CER processes during the task (AD+, n = 16) and AD patients who did not (AD–, n = 10). These two groups of patients did not differ significantly with regard to age [$t(24) = .24$; $p = .82$], years of education [$t(23) = .87$; $p = .39$] or total score on the Mattis Dementia Rating Scale [$t(24) = .7$; $p = .47$]. Age, years of education and scores on different subtests of the Mattis Dementia Rating Scales in the two groups of AD patients are reported for the reader's information in Table 1 (even though there was no significant between-group difference). The mean proportions of correct answers for each type of pair in each group are shown in Table 2. All participants had more hits for intact pairs than false alarms for novel pairs, suggesting that all participants were able to discriminate between studied materials (items and/or pairs) and unstudied ones. An ANCOVA with age as covariate revealed a main effect of group on the proportion of Hits for intact pairs [$F(2,39) = 3.65$; $p = .04$], on the proportion of correct rejections of recombined pairs [$F(2,39) = 7.03$; $p = .003$] and on the proportion of correct rejections of novel pairs [$F(2,39) = 8.47$; $p = .0009$]. The results of post hoc tests (Newman-Keuls tests) are presented in Table 2. Mean reaction time in seconds was $3.14 \pm .30$ in the AD– group, $3.76 \pm .25$ in the AD+ group and $2.92 \pm .41$ in the HC group. An ANOVA with repeated measures and age as covariate revealed that there was no main effect of response type [$F(5,125) = .96$; $p = .46$], no main effect of group [$F(2,25) = 2.32$; $p = .12$] and no interaction effect of response type with group [$F(10,125) = .13$; $p = .99$] on reaction times.

Estimated proportions of CER and familiarity processes in the three groups are illustrated in Figure 2. ANCOVAs conducted on estimated proportions of CER and familiarity in the three

groups of participants when controlling for age indicated that group had no significant effect on estimated proportion of familiarity [$F(2,39) = .66$; $p = .52$], whereas it had a significant effect on estimated proportion of CER [$F(2,39) = 19.80$; $p < .001$]. Post hoc tests (Newman-Keuls tests) revealed that the estimated proportion of CER was significantly lower in the AD+ and AD– groups than in the HC group (both p's $< .001$) and that (as expected per the experimental design) the estimated proportion of CER was significantly lower in the AD– group than in the AD+ group ($p < .05$).

Functional MRI Results

Item Familiarity

The conjunction analysis of the mean brain activity associated with correct recognition of intact pairs and false alarms for recombined pairs (with an exclusive masking of brain activations related to correct rejection of novel pairs) in the HC, AD+ and AD– groups revealed activations along the intraparietal sulcus (IPS) bilaterally and in the left cerebellum (Table 3 and Figure 3).

The conjunction analysis of the mean brain deactivation associated with correct recognition of intact pairs and false alarms for recombined pairs (with an exclusive masking of brain deactivations related to correct rejection of novel pairs) in the HC, AD+ and AD– groups yielded no significant result.

Regarding the contrast of Hit_IP and CR_RP, no region was found to be commonly activated by all three groups (i.e. no common activation related to common processing of information).

Pair CER

The conjunction analysis in the HC and AD+ groups of activation that was greater for correct recognition of intact pairs than for false alarms to recombined pairs revealed activation in the inferior precuneus/posterior cingulate cortex (PCC, Table 4 and Figure 4). Moreover, Figure 5 shows that activity in this region was related only to controlled episodic retrieval of intact (previously associated) pairs of words (hits), and not to any other cognitive processes in the task (correct rejection of recombined pairs, false recognition of recombined pairs or correct rejection of new pairs).

No region was found to be significantly more activated in HC than in AD+ and vice versa at the selected threshold when performing direct statistical comparisons (respectively, HC > AD+ and AD+ > HC).

PPI analyses revealed that the inferior precuneus/PCC was positively connected with the left hippocampus, the left DLPFC and the right inferior posterior parietal cortex during pair CER in HC participants more than in AD patients (Table 5 and Figure 6). No region was found to be more significantly connected to the inferior precuneus/PCC in AD patients than in HC during pair CER.

IV. Discussion

Studies of long-term memory have suggested that some memory functions are more altered than others in Alzheimer's disease. In particular, the multiple aspects of the recollection function appear to be more globally and more severely affected in AD than the familiarity function. However, little is known about the brain substrates of these alterations. In this study, the PDP (Jacoby, 1991; Jacoby et al., 1993) was applied to a word-pair memory task and administered to mild AD patients and healthy older participants in an fMRI scanner to

identify the cerebral substrates of associative controlled aspects of recollection and of item familiarity in AD. Our procedure does not exclude (but did not evaluate) other aspects such as subjective experience and contextual retrieval to be engaged during memory retrieval. Therefore our procedure made it possible to investigate the brain regions directly involved in associative CER and explore the brain regions closely related to this process in healthy older and AD participants.

Impaired Associative CER and Preserved Item Familiarity in Alzheimer's Disease

The behavioural results showed that, whereas familiarity estimates were similar across groups, some AD patients had no controlled retrieval at all while others had some CER abilities although they were significantly poorer than those of healthy older participants. This suggests that familiarity, as measured by our task, was relatively preserved whereas CER was significantly altered in our AD patients. Our results are consistent with previous studies showing that CER is severely altered in AD patients (Adam et al., 2005; Knight, 1998; Smith and Knight, 2002) and with a previous study showing that associative recognition is impaired in these patients (Hanaki et al., 2011). Our results are also consistent with Gallo et al.'s (2004) findings (which were obtained with a analogous procedure) that AD patients have difficulties engaging controlled recall of the correct association in order to reject recombined pairs, which leads to familiarity-based false recognition. Previous studies using process-dissociation procedures to disentangle recollection- and familiarity-based performance have found impaired familiarity in AD patients (Ally et al., 2009a; Wolk et al., 2011). On the other hand, studies that have contrasted CER and automatic memory retrieval found that automatic processes were relatively preserved or, at least, less impaired than CER (Adam et al., 2005; Knight, 1998; Smith and Knight, 2002). Together, these results might suggest that familiarity is a complex function that can support item retrieval in some situations but not in others in

AD patients. From this perspective, Embree et al. (2012) found that patients with aMCI had impaired familiarity when the stimuli were words but not when they were pictures. Ally et al. (2009) obtained similar results. They suggested that conceptual priming and perceptual fluency might support an intact sense of familiarity for pictures in these patients. In the same vein, Wolk et al. (2005) found that patients with mild AD were able to use conceptual fluency in their word recognition judgements. These results suggest that, under some conditions (but not others), the underlying mechanisms of the familiarity function may drive normal item retrieval. Further studies are needed to determine under which conditions and at which stage of disease these processes are able to support normal item recognition.

As associative CER and item familiarity are differentially affected by the pathological process in AD, they are expected to be supported by different brain regions.

Familiarity and Parietal Cortex

The imaging results revealed that familiarity was related to parietal activation along the intraparietal sulcus (IPS) in both healthy older and AD participants. This region is part of an attentional or task-positive network (Fox et al., 2005). Brain activations around the IPS related to familiarity have also been frequently found in the healthy population (Ciaramelli et al., 2008). The location of this peak of activation is congruent with previous fMRI findings, showing that dorsal parietal activations during memory tasks tend to be in the lower part of this region, that is, the lateral bank of the IPS (Cabeza et al., 2011; Hutchinson et al., 2009). Interestingly, in our study, this parietal activation was commonly found in healthy older participants and in AD patients who had residual recollection abilities but also in AD patients without any residual recollection abilities. This suggests that, in AD patients, intact familiarity for individual items is supported by the brain region that usually supports familiarity in the healthy population, even when controlled memory retrieval is completely

disrupted. According to Ciaramelli et al. (2008), the region around the intraparietal sulcus is active in memory tasks when top-down assistance with memory retrieval is needed. In our study, this region was active when participants experienced item familiarity that led either to correct acceptance of an intact pair or to incorrect acceptance of a recombined pair. Therefore, we suggest that the IPS supports an automatic memory process that leads to the acceptance of an item as old without controlled retrieval of the target information (see also Collette et al., 2005, on the role of the IPS in basic attentional processes). Together, the imaging and behavioural results of familiarity suggest that this automatic memory process is still efficient in our AD patients. Since parietal involvement is related to both correct recognition of an intact pair and a false alarm for a recombined pair, it might also reflect subjective feelings of associative retrieval, which do not guarantee accurate/correct recognition. However, at present, there is little evidence to support this assumption in the literature and no evidence that this cognitive process is preserved in AD patients.

The brain regions related to item familiarity were also explored by performing a contrast between correct recognition of intact pairs (i.e. ‘old’ responses to intact pairs, Hit_IP) and correct rejection of recombined pairs (i.e. ‘new’ responses to recombined pairs, CR_RP). Since correct recognition of intact pairs is considered to be supported by associative CER and item familiarity processes, whereas correct rejection of recombined pairs is assumed to be driven by controlled retrieval of the correct association (i.e. a recall-to-reject process), subtracting brain activations for CR_RP from brain activations related to Hit_IP should isolate the brain activations related to familiarity. However, ‘new’ responses to recombined pairs may also be driven by the absence of familiarity/recollection. In these cases, subtracting brain activations for CR_RP from brain activations related to Hit_IP may reveal brain activations related to both familiarity and associative CER. That is, at the subject level, the

contrast might isolate familiarity, CER, or both familiarity and CER. Similarly, at the group level, the contrast may mainly isolate familiarity in some participants, whereas in others, it may mainly isolate CER or both familiarity and CER. In an attempt to deal with this problem, at the group level, we examined only brain activations that were common to healthy older controls (HC group), AD patients who showed residual CER abilities (AD+ group) and AD patients without residual CER abilities (AD– group). This conjunction analysis at the group level was intended to rule out any brain activations related to CER. However, it did not yield any significant results. We suggest that the non-significant results may be due to the fact that the activations examined by the analysis are not consistent within subjects and between subjects, since in some cases the contrast isolated familiarity whereas in other cases it isolated both familiarity and CER; as a result, it lacks statistical power. Furthermore, CR_RP can be based on controlled retrieval of the correct association accompanied by familiarity for individual items since the two processes are not mutually exclusive. If we consider that Hit_IP may be supported by both familiarity and CER and that CR_RP can be based on CER accompanied by item familiarity, we expect that subtracting brain activations for CR_RP from brain activations related to Hit_IP may yield no results. Therefore this second hypothesis can also account for the absence of significant results when contrasting Hit_IP and CR_RP.

Between-group comparisons during associative CER.

One might be surprised that statistical between-groups comparisons of brain activation related to correct retrieval of intact pairs when compared to incorrect recognition of recombined pairs (i.e. during associative CER) yielded no significant result. In particular, one may be surprised that this contrast did not reveal any activity in the hippocampus in healthy older participants when compared to AD patients. However, our PPI results subsequently

demonstrated that activity in the hippocampus correlated with activity in the Inferior Precuneus/Posterior Cingulate Cortex (PCC) during recollection in healthy older participants more than in AD patients. This suggests that the hippocampus does play a role in the recollection function of healthy older participants. The fact that a simple statistical contrast did not reveal any activity in the hippocampus whereas psychophysiological interaction analysis revealed that the hippocampus is co-activated with the PCC during recollection suggests that activity in the hippocampus is highly variable in healthy participants and therefore can not be easily put in evidence by using a simple direct contrast. Most of studies that highlighted the role of the hippocampus in associative memory and in recollection were focused on the MTL. For example, the only study that has examined the neural correlates of recollection and familiarity functions in AD patients, that is, Wolk and collaborators' study (2011), was focused on the MTL. In contrast, the aim of our study was to examine the recollection function in AD patients within and beyond the MTL as episodic memory is supported by a broad brain network. In consequence, our experimental task has not been designed to maximize the engagement of the hippocampus in healthy older participants. Indeed, the role of the hippocampus in within-domain associations is debated in the scientific literature (for a brief overview of theories of associative memory see introduction). In contrast, most of the current views agree that retrieval of between-domain associations is supposed to engage the hippocampus. Therefore, strong and direct engagement of the hippocampus would have been more likely to appear with a between-domain association material such as face-name association. Finally, the fact that the hippocampus was not significantly activated in the "hits to intact pairs – false recognition of recombined pairs" contrast could make sense of one considers previous studies that have found that recollection-related activity in the hippocampus was reduced in healthy aging (Daselaar et al., 2006; Denis et al., 2008). In fact, it has been proposed that changes in episodic memory in healthy aging

originate partially from alterations in associative processes reflecting senescent changes in the medial temporal lobe (Shing et al., 2010).

Associative CER and the Inferior Precuneus/Posterior Cingulate Cortex

CER was associated with activations in the inferior precuneus/posterior cingulate cortex (PCC) both in healthy older participants and in AD patients who showed some CER abilities. This region is typically activated in PET and fMRI studies of episodic retrieval (Cabeza and Nyberg, 2000). More specifically, the PCC has been found to be activated during correct source recognition (Lundstrom et al., 2005) and during the experience of remembering in healthy participants (Eldridge et al., 2000; Henson et al., 1999a; Wheeler and Buckner, 2004; Woodruff et al., 2005; Yonelinas et al., 2005). In a recent meta-analysis, Kim (in press) has confirmed that the left precuneus and the bilateral PCC are associated with a greater 'old' effect during a source-retrieval task than during an item-retrieval task. Moreover, Lundstrom et al. (2005) and Woodruff et al. (2005) showed that activation of the PCC during memory retrieval was not related to the nature of items (viewed versus imagined, studied words versus names of studied pictures), suggesting that the PCC is content-insensitive. However, at present, little is known about the precise role of the precuneus/PCC in episodic memory retrieval.

In our study, the inferior precuneus/PCC was activated only when the participants correctly recognised the accurate association of words from the encoding context (e.g. 'mouse and factory together') and did not erroneously accept the previously encoded information that had been falsified ('hospital scissors' instead of 'hospital lion' and 'moon scissors'). This suggests that the PCC plays an important role in the controlled retrieval of previously encoded associations that constitutes the successful recollection of episodic memories. One might also hypothesise that it is not the controlled aspect that drives inferior precuneus/PCC

activation but rather the associative aspect. The results of previous studies are congruent with both interpretations. The problem is that recollection and associative memory are such close concepts that we cannot easily adjudicate between these two interpretations of inferior precuneus/PCC activation in our task. However, based on the design of our study, we can state that inferior precuneus/PCC activation is only related to accurate controlled retrieval of associations. Since this activation is not observed in false alarms for recombined pairs, it does not seem to be related to a subjective feeling of association or correct (non-controlled) retrieval of individual items.

Several connectivity analyses have shown that the precuneus/PCC is one of the most globally connected regions (Andrews-Hanna et al., 2010; Buckner et al., 2009; Cole et al., 2010; Fransson and Marrelec, 2008). Therefore, one may assume that the PCC may play a role in episodic retrieval by functionally interacting with other regions, such as the hippocampus. This may explain why the exact role of this region in memory retrieval cannot be easily determined.

It is well known that the PCC is subject to significant atrophy and metabolic abnormalities early in AD (Salmon et al., 2009; for a review, see Buckner et al., 2005). In fact, it is one of the brain regions most affected by AD, even at the very early clinical manifestations of the disease (Salmon et al., 2008; for reviews, see Buckner, 2004 and Sperling et al., 2010). PET studies showed that episodic memory retrieval is correlated with brain metabolism in the PCC in AD patients (Desgranges et al., 1998, 2002), as well as in patients with MCI and questionable AD (Chételat et al., 2003; Salmon et al., 2008). More recently, Bastin et al. (2010) showed that CER performance, as assessed by the PDP, was related to metabolism in the PCC in pre-dementia stage AD patients. In the same vein, using fMRI, it has been found

that activation in the PCC was significantly correlated with episodic retrieval success in a sample including healthy elderly participants, elderly participants with MCI and AD patients (Heun et al., 2006). In addition, fMRI studies have reported decreased activation in the PCC during episodic retrieval in patients with MCI in comparison to healthy older participants (Johnson et al., 2006; Ries et al., 2006; Trivedi et al., 2008). Thus, both PET and fMRI studies suggest that functional perturbations in the PCC may play an important role in the impairment of episodic memory retrieval shown by AD patients, even at a very early stage. Our results showed that the role of the PCC in memory retrieval is specific to the successful, controlled retrieval of associative information in healthy older participants. Moreover, when this process can still be residually recruited by certain AD patients, it is similarly supported by the PCC. Therefore, one might speculate that PCC alterations may play a role in impaired associative controlled retrieval of episodic information in AD patients who do not objectively show residual recollection abilities. However, the design of our study does not allow us to directly examine this hypothesis.

Functional Connectivity During Associative CER

Since complex functions such as recollection and familiarity should be underlain by the coordination of a number of simple processes supported by different interconnected regions (Montaldi and Mayes, 2010), we examined functional connectivity during episodic retrieval in our participants. The results of the PPI analyses revealed that, in healthy older participants (and not in AD+ patients), the inferior precuneus/PCC was functionally connected to the hippocampus, the inferior parietal cortex and the DLPFC specifically during successful controlled retrieval of the association. The hippocampus has been found to be engaged during retrieval of word pairs (Giovanello et al., 2004, 2009; Meltzer and Constable, 2005; Prince et

al., 2005; Stark and Squire, 2001), face-name associations (Kirwan and Stark, 2004; Small et al., 2001), face-object associations (Ranganath et al., 2004a), face-spatial location associations (Duzel et al., 2003) and retrieval of an item with its learning context (Slotnick, 2010; Yonelinas et al., 2001). These findings support the idea that the hippocampus plays a role in the use of relational information in declarative memory (Preston et al., 2004). It is not surprising that the hippocampus is engaged through functional connectivity with the PCC in successful retrieval in our task, since this task is characterised by associative material. However, this does not imply that the relational role of the hippocampus in this task is restricted to the experimental associations; hippocampal involvement may also reflect retrieval of other associated details from the encoding context such as thoughts and mental images.

There is currently no strong evidence for assuming that the retrieval of associations supported by the hippocampus is conscious and controlled. On the contrary, the hippocampus has sometimes been thought to support the phenomenon of *ecphory,* which corresponds to the automatic retrieval of information associated with the cue (Moscovitch, 1992). In this regard, Montaldi et al. (2006) have shown that involuntary recollection activates the hippocampus. Thus, the functional connectivity between the inferior precuneus/PCC and the hippocampus found during recollection in healthy participants in our task might reflect the interaction between the associative controlled retrieval mode, supported by the PCC, and the retrieval of episodic associations, supported by the hippocampus. We found that this functional connectivity was impaired in our AD patients, although they showed some CER abilities. This finding suggests that even when AD patients have controlled episodic retrieval abilities, the complex retrieval of spontaneous associations may be impaired and successfully retrieved memories may lack contextual details. This assumption is congruent with previous findings

that the recall of AD patients is characterised by poor contextual details even when probes are provided to encourage greater recall of details (Irish et al., 2011a, 2011b).

Regarding the inferior parietal cortex, some authors have suggested that it supports bottom-up attention to memory, that is, the capture of attentional resources by relevant memory cues and/or recovered memories (Cabeza, 2008; Cabeza et al., 2008; Ciaramelli et al., 2008). Others have proposed that the inferior and posterior parietal cortex serves as an 'episodic buffer' by representing information in a form accessible to decision-making processes (Wagner et al., 2005). However, this latter hypothesis does not clearly account for the results of meta-analyses showing that, within the parietal lobe, familiarity is preferentially associated with the superior parietal cortex whereas recollection is preferentially associated with the inferior parietal cortex (Kim, 2010; Skinner and Fernandes, 2007). It has recently been proposed that the parietal lobe supports the subjective experience of recollection or a similar aspect of recollection, the feeling of confidence (Ally et al., 2008; Berryhill et al., 2007; Davidson et al., 2008; Hayes et al., 2011; Slotnick, 2010). Simons et al. (2010) reported that patients with bilateral parietal lesions have impaired subjective recollection but preserved bottom-up attention processes during memory tasks. According to these authors, during memory retrieval, the parietal cortex is responsible for the subjective experience of richness, vividness and confidence in one's recollection that constitutes the sense of personal experience in the recollection function. From that point of view, functional connectivity between the inferior precuneus/PCC and the inferior parietal cortex during episodic retrieval in healthy participants in our task may reflect the interaction between controlled and objectively successful associative retrieval, supported by the inferior precuneus/PCC, and the sense of personal experience associated with recollection, supported by the inferior parietal cortex.

We found that this functional connectivity was deficient in our AD patients during episodic memory retrieval. Therefore, we might speculate that, when AD patients are able to engage controlled associative memory retrieval, the process might not be associated with the sense of personal experience. In other words, we might hypothesise that, even when AD patients objectively show CER abilities, the recollection function may lack autonoesis. Accordingly, as mentioned in the introduction, subjective experience of recollection has frequently been found to be reduced in AD patients (Dalla Barba, 1997; Piolino et al., 2003; Rauchs et al., 2007). Moreover, there is evidence of impoverished vividness and self-referential imagery, constituting impoverished autonoetic consciousness, during the recall of autobiographical memories by AD patients (Irish et al., 2011b). However, other hypotheses concerning the role of the parietal cortex in episodic retrieval might also be compatible with the alteration of functional connectivity between the inferior precuneus/PCC and the inferior parietal cortex during successful CER in AD patients. Thus, further studies are needed, first to adjudicate between these views and second to characterise the more subtle deficits in AD patients' episodic retrieval profile.

Finally, the DLPFC has frequently been found to be activated during recollection (Kim, in press; Spaniol et al., 2009) and may be responsible for the monitoring or evaluation of recovered content (Dobbins and Han, 2006; for reviews, see Fletcher and Henson, 2001, and Simons and Spiers, 2003). When potential episodic elements are retrieved, monitoring operations supported by the DLPFC are recruited to assess whether they are accurate or not. This might require source verification and rejection of the retrieved representations if these do not match the retrieval criteria (Simons and Spiers, 2003). Accordingly, the functional connectivity between the inferior precuneus/PCC and the DLPFC during recollection in

healthy participants in our task may reflect the interaction between controlled associative retrieval, supported by the PCC, and post-retrieval verification processes, supported by the DLPFC. We found that this functional connectivity was impaired during associative CER in AD patients. This finding suggests that the engagement of monitoring processes during episodic retrieval might be deficient in these patients. One can speculate that the retrieval of episodic elements supported by the inferior precuneus/PCC and its functional connectivity with the hippocampus is inadequately verified in AD patients due to the functional disconnection between the DLPFC and the inferior precuneus/PCC in these patients. This may result in inaccurate memories such as intrusions in recall or false alarms in recognition tests. This hypothesis is congruent with the profile of responses for novel items in AD patients in our task. Indeed, the behavioural results revealed that our AD patients rejected significantly fewer unseen items (i.e. novel pairs) than the HC participants did. In other words, AD patients tended to inaccurately accept new items as memories (false alarms). This false memory phenomenon has often been reported in AD patients (Plancher et al., 2009; for a review, see Ergis and Eusop-Roussel, 2008). Recently, Gallo et al. (2010) found that false recognitions in AD were associated with medium to high levels of confidence. This finding suggests that AD patients' false memories are not yielded by a guessing process but rather might be the result of a modified recollection function.

In summary, capitalising on previous studies, we hypothesise that, even when AD patients have successful associative controlled memory retrieval abilities related to inferior precuneus/PCC activation, the recollection function lacks autonoetic quality and episodic details, due to altered functional connectivity between the inferior precuneus/PCC, the hippocampus and the inferior parietal cortex. In addition, AD patients might experience false memories due to impaired functional connectivity between the inferior precuneus/PCC and

the DLPFC during the episodic retrieval process. However, the subjective experience of recollection and the content of remembering could not be assessed in our participants when they were performing the task in the fMRI scanner, so our hypothesis regarding the consequences of impaired functional connectivity during controlled retrieval could not be directly examined in this study. Further studies are needed to closely examine the complex quality of recollection and its neural correlates in AD patients.

Limitations

Based on the idea that correct recognition of an intact pair may be supported by both controlled retrieval of the pair and item familiarity for individual items, whereas false recognition of a recombined pair may be driven by item familiarity without controlled access to the true pair, we isolated brain activity related to associative CER by contrasting correct recognitions of an intact pair with false alarms for recombined pairs.

One criticism that may be made of this contrast is that correct recognition of an intact pair might also be supported by associative familiarity. Indeed, according to the DD view (Mayes et al., 2007), recognition of a pair of words may be supported by associative familiarity. However, the authors also suggested that, if the association was encoded using a mediator, recollection is needed to retrieve the target association via the mediator. In the present study, at the encoding phase, the participants were told to form a mental image in which the two items interacted. In this context, correct recognition of an intact pair is likely to engage retrieval of the mediator, that is, the mental image formed in the encoding phase, and therefore to be supported by recollection rather than by associative familiarity. In addition, our imaging data also suggest that correct recognition of an intact pair and a false alarm to a recombined pair engage different functions since only the former is related to inferior

precuneus/PCC activation and functional connectivity with the recollection-related regions such as the hippocampus in healthy older participants. If correct recognition of intact pairs were supported by associative familiarity whereas false alarms to recombined pairs were supported by item familiarity, our contrast should have isolated brain activation specifically related to associative familiarity and not for 'simple' item familiarity. Since there is currently little evidence that associative familiarity and item familiarity are independent functions supported by distinct brain networks, it does not seem likely that the brain network revealed by our contrast is specifically related to within-domain associative aspects of familiarity.

Another possibility that should be considered is that false alarms for recombined pairs might be driven by recollection of the individual items without controlled access to the original association. If this was the case, our contrast might isolate brain regions specifically involved in recollection of a given association but not related to recollection of an item and the other details from the encoding context (such as thoughts). Since there is currently little evidence that recollection of a specific association and item recollection are independent functions supported by two distinct brain networks, it does not seem likely that the brain network revealed by our contrast is specifically related to a particular experimental within-domain associative aspect of recollection, even though this hypothesis cannot be ruled out.

Some studies suggest that true and false recognitions are associated with similar patterns of activity in the brain. In particular, several studies suggest that false recognitions may be related to medial temporal metabolism or activation (Gutchess and Schacter, 2012; Moritz et al., 2006; Schacter et al., 1996, 1997), but also to activation in the posterior cingulate cortex, prefrontal cortex and amygdala (Abe et al., 2008; Garoff-Eaton et al., 2006; Gutchess and Schacter; 2012; Lidaka et al., 2012; Moritz et al., 2006; Schacter et al., 1997). In the same

vein, Kuraman and Maguire (2006) have shown that the hippocampus is activated when there is a mismatch between the currently presented stimulus and the one previously encoded (e.g. a change in the temporal sequence). According to these authors, the hippocampus detects associative mismatches between what is expected, based on retrieval of past experience, and current input. Our CER contrast eliminates brain activations that are common to correct recognition of intact pairs and incorrect recognition of recombined pairs to isolate brain activations that are specifically related to correct recognition of the original pair. Therefore, one may argue that, on the one hand, this contrast is highly specific, but on the other hand, this contrast may prevent one from observing the brain regions usually associated with recollection such as the hippocampus because these regions are also engaged during false memories. In point of fact, although it was not actually the aim of this study, our 'item familiarity' contrast tested this hypothesis. We examined brain regions commonly activated by both correct recognition of an intact pair and false recognition of a recombined pair. However, this analysis did not reveal any significant activation in the recollection-related and false-memory regions such as the hippocampus.

Finally, the basic assumptions on which the PDP depends should be carefully considered. The PDP assumes that recollection and familiarity are independent functions. In this view, a wide range of evidence suggests that recollection and familiarity operate independently at retrieval (see Yonelinas et al., 2002, for a review). Similarly, recognition judgements for item and associative information have been found to be dissociated (Yonelinas, 1997). In the current study, controlled retrieval of 'word pairing', as a core aspect of recollection, was contrasted to familiarity-based acceptance of recombined pairs. To our knowledge, no study has rigorously and directly examined whether these two particular processes are completely independent. However, based on previous findings concerning recollection/associative

memory and familiarity/item memory, one can reasonably consider that the two aspects that have been opposed in this study are independent, although future studies are needed to affirm a double dissociation between those aspects.

Conclusion

This is the first study to directly examine whole brain regional activity engaged during one core aspect of recollection, namely associative controlled episodic retrieval contrasted to item familiarity, in AD patients. We found that CER is severely impaired whereas item familiarity is preserved in our patients. The preserved automatic detection that an item is old (but that does not permit patients to accurately retrieve encoded information) is related to a parietal region centred on the IPS in patients as in the healthy population. In contrast, residual associative controlled memory retrieval in AD patients is related to inferior precuneus/PCC activation, also as in healthy participants. However, we found altered functional connectivity between the inferior precuneus/PCC and the inferior parietal cortex, the hippocampus and the DLPFC in AD patients during recollection, suggesting that residual recollection in these patients might be impoverished by the lack of some recollection-related aspects such as autonoetic quality, episodic details and verification. Therefore, future studies are needed to carefully examine the different aspects of recollection in AD patients.

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Figure 1. Examples of stimuli in the experimental paradigm. Screens are separated by a fixation cross not represented here.

Figure 2. Familiarity and CER proportions in the three experimental groups.
Standard errors are represented by error bars. *$p < .000005$.

Figure 3. Brain regions related to item familiarity in AD–, AD+ and HC groups. $p < .05$ corrected for the whole brain volume at the cluster level.

Figure 4. Brain regions related to CER in AD+ and HC groups. $p \leq .05$ corrected for the ROI volume at the voxel level.

Figure 5. Mean parameter estimates in PCC [MNI coordinates: –10 –50 40]. Baseline, baseline events; Hit_IP, correct recognition of intact pairs; CR_RP, correct rejections of recombined pairs; FA_PR, false alarms for recombined pairs; CR_NP, correct rejections of novel pairs. Mean parameters have not been calculated for false alarms for novel pairs (FA_PN) because the number of FA_PN was too small in most of the HC participants.

Figure 6. Regions that are functionally connected to the posterior cingulate cortex during CER in healthy older participants compared to AD patients (yellow). The blue dot represents the location of the physiological variable (PCC).

Footnotes:

[1]*Note: As suggested by Montaldi & Mayes (2010), the concept of unitization has some methodological limitations since, notably, there is, at present, no objective criterion for measuring unitization.*