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

Sarah Genon^a, Fabienne Collette^a, Dorothee Feyers^b, Christophe Phillips^{a,c},
Eric Salmon^{a,d,1} and Christine Bastin^{a,*,1}

^aCyclotron Research Centre, University of Liège, Belgium

^bDepartment of Senescent Psychology, University of Liège, Belgium

^cDepartment of Electrical Engineering and Computer Science, University of Liège, Belgium

^dMemory Centre, CHU Liège, Belgium

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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 (HCs) 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 auto-noetic quality, episodic details and verification.

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* Corresponding author. Cyclotron Research Centre, University of Liège, Allée du 6 Aoit, B30, 4000 Liège, Belgium.

E-mail address: Christine.Bastin@ulg.ac.be (C. Bastin).

¹ Eric Salmon and Christine Bastin equally contributed.

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1. 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](#); [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 focussing on the distinction between recollection and familiarity have mainly used process-estimation methods, such as the process dissociation procedure (PDP) and the Remember/Know (R/K) procedure. The 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 R/K 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 MCI 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 auto-noesis, that characterized episodic retrieval. According to [Tulving \(2002\)](#), the term auto-noetic has been used to refer to this special kind of consciousness that allows us to be aware of subjective time in which events happened. Auto-noetic awareness (or auto-noesis) is required for remembering, to re-experience, through auto-noetic awareness, one's own previous experiences ([Tulving, 2002](#)). Accordingly, [Irish et al.](#) concluded that AD patients have impoverished auto-noetic 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

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