

**Neural correlates of controlled memory processes in questionable Alzheimer's disease**

## Abstract

Alzheimer's disease (AD) is characterized by a progressive loss of controlled cognitive processes (processes requiring mental effort and attentional resources), and functional neuroimaging at early stages of AD provides an opportunity to tease out the neural correlates of controlled processes. Controlled and automatic memory performance was assessed with the Process Dissociation Procedure in 50 patients diagnosed with questionable Alzheimer's disease (QAD). The patients' brain glucose metabolism was measured using FDG-PET. After a follow-up period of 36 months, 27 patients had converted to AD, while 23 remained stable. Both groups showed a similar decrease in controlled memory processes but preserved automatic processes at entry into the study, suggesting that impairment of controlled memory would not be specific for AD. Patients who subsequently converted to Alzheimer type dementia showed significantly decreased brain metabolism at baseline compared to stable QAD in associative cortices known to be involved in AD (the left precuneus, the right inferior parietal lobule and bilateral middle temporal cortex). Voxel-based cognitive and metabolic correlations showed that a decrease in controlled memory processes was preferentially correlated with lower activity in the dorsomedial prefrontal and posterior cingulate cortices in very early AD patients. The dorsomedial prefrontal cortex would play a role in controlled memory processes as they relate to reflective and monitoring processes, while the posterior cingulate cortex is involved in the controlled access to previously encoded episodes. In stable QAD patients, reduced controlled performance in verbal memory correlated with impaired activity in the left anterior hippocampal structure, which would alter the reactivation of associations created at encoding.

## 1. Introduction

In Alzheimer's disease (AD), controlled processes –processes requiring mental effort and attentional resources [1]- are affected early in the course of the disease, whereas automatic processing is relatively preserved in the early stages [2]. Even before the diagnosis of AD, future demented patients already present a specific disruption of controlled processes [3-4]. In the memory domain, AD patients typically show impairments in controlled, explicit memory tasks, such as recall or recognition tests [5]. In contrast, implicit (more automatic) memory tasks, such as priming, are better preserved, although contradictory results have been reported [6]. The ambiguity of the findings concerning implicit memory in AD may stem from the contamination of priming tasks by the use of explicit memory strategies. To overcome this contamination problem, Jacoby developed a paradigm (the Process Dissociation Procedure) that allows one to estimate the separate contributions of controlled versus automatic processes within a single verbal memory task [7]. The distinction is made possible by a comparison of two conditions (inclusion and exclusion) of word-stem completion in which these processes operate in different ways. Typically, in the inclusion condition, both controlled and automatic processes lead to the retrieval of a studied item. In the exclusion condition, automatic and controlled processes work in opposition, with the former leading to an erroneous answer, and the latter helping to consciously avoid it. Mathematical equations (described in the Methods section below) applied to the data provide separate estimates of the contributions of controlled and automatic memory processes. With this procedure, Adam et al. [8] confirmed the significant deterioration of controlled processes and the integrity of automatic processes in early AD patients.

Functional imaging is well suited to examine the neural correlates of controlled memory processes, as estimated by the Process Dissociation Procedure, in AD. Previous studies of correlation between cerebral activity and recall or recognition performance in AD

have related explicit memory processing to a network of frontal, posterior associative and limbic regions [9-10] (see [11], for a review of PET studies in AD). This suggests that the memory deficit in AD is not exclusively associated with a specific dysfunction of the medial temporal region, although that structure plays a central role in episodic memory [12] and is affected early in the course of the disease [13].

In this context, the aim of the present study was to tease out the neural correlates of controlled memory processing in AD. To disentangle consciously controlled from automatic memory processes, we adopted the Process Dissociation Procedure with a word stem completion task [14]. Moreover, because it has been suggested that a deficit affecting the controlled aspects of cognition may represent an early indicator of dementia [4], the study focused on the very early stages of AD. More specifically, we selected patients who were clinically characterized by a cognitive dysfunction that did not significantly disrupt their activities of daily living. Although the patients did not meet the criteria for dementia, they might still be in a very early stage of AD (questionable Alzheimer's disease or QAD [15]). It has been shown that many such patients progress to dementia in the following years [16-17].

Therefore, the current study using the Process Dissociation Procedure examined whether QAD patients present the same profile of impaired controlled memory processes and preserved automatic memory processes as early AD patients [8]. Moreover, the patients were followed up for 36 months in order to identify those who converted to AD. This allowed us to retrospectively compare future converters and stable QAD patients with regard to their performance on controlled and automatic memory components.

Among the risk factors associated with conversion to dementia, the level of education has been put forward in the cognitive reserve hypothesis [18]. According to this hypothesis, individuals with a high level of education have a reduced risk of developing Alzheimer's disease, possibly because they can optimize the efficiency of brain networks so that the

impact of brain pathology is limited on their cognitive performance. As most studies examined the influence of educational level on the onset of AD in community-base cohorts of elderly people [19-20], little is known on the effect of cognitive reserve in the conversion of QAD to AD. Moreover, even when dementia is diagnosed, cognitive deterioration differs as a function of education, with low-educated AD patients presenting with greater memory and attention deficits than high-educated patients [20]. So, we examined the influence of education level on controlled and automatic memory processes in QAD as a function of the clinical outcome.

Finally, images of the patients' brain glucose metabolism were obtained with FDG-PET. Voxel-based cognitive-metabolic correlations were used to identify the regions where metabolism was positively correlated with controlled memory processes in the QAD patients who subsequently went on to develop AD and those who remained stable in the following 36 months. Such analyses should help us to better understand the cerebral modifications underlying the decline in controlled memory processes in QAD, and specifically to clarify whether the neural correlates of controlled processes in the early stages of AD still involve the medial temporal lobe, which is already quite affected in early AD [13] or include frontal and posterior associative regions, as previously suggested [11].

## 2. Materials and Methods

### 2.1. Participants

The study included 50 QAD patients (28 women) who were referred by neurologists working in memory clinics. Their mean age was 69 years old ( $SD = 7.6$ ). The patients had completed an average of 11.5 years of education ( $SD = 4.0$ , range 5-22). Patients were classified as having a high educational level if they achieved at least a short secondary school levels (9 years of education), whereas they were classified as having a low educational level if

they had a primary school level or less (less than 9 years of education, cf. [20]). They were selected on the basis of general examination, neurological and neuropsychological assessments, laboratory evaluation and structural neuroimaging. No subject had mental retardation, less than 4 years of education, brain trauma, epilepsy, cancer, depression, any major systemic disease or any substance abuse.

On the Clinical Dementia Rating (CDR) scale, the patients were all at stage 0.5, corresponding to questionable dementia with impaired memory, but preserved everyday skills, activities and self-care [15]. The neuropsychological profile of the patients was also compatible with the criteria for amnesic mild cognitive impairment (aMCI) proposed by Petersen et al. [17, 21]: memory complaints confirmed by a relative, memory deficits for their age and education (that is, performance 1.5 standard deviations below the mean of matched controls on at least one memory test), possibly additional cognitive dysfunction in another non-memory domain (42 amnesic single-domain MCI and 8 amnesic multiple-domain MCI), relatively preserved general cognitive function, preserved activities of daily living, and no dementia. Structural neuroimaging showed mild atrophy or mild leukoaraiosis, at most. All patients had Mini Mental State Examination (MMSE) scores of 22 and over.

At inclusion, they performed the experimental task and underwent a positron emission tomography examination using ( $^{18}\text{F}$ )fluoro-2-deoxy-D-glucose (FDG-PET). Both the experimental task and the FDG-PET were performed on the same day. Every 6 months, the QAD patients were re-evaluated with a neuropsychological battery, either until conversion or until 36 months had elapsed.

At the end of a follow-up of 36 months, 27 patients converted to dementia, meeting the criteria for AD [22] and 23 remained stable QAD. Conversion was seen in 6 multiple-domain aMCI patients (75 %) and 21 single-domain aMCI patients (50 %). On average, conversion occurred 14 months ( $SD = 9.8$ ) after the initial testing. Interestingly, most

conversions occurred within 6 months ( $n = 11$ , including 3 multiple-domain aMCI) and 12 months ( $n = 8$ , including 3 multiple-domain aMCI). Three patients converted after 18 months, 3 after 30 months and 2 after 36 months. The cumulative frequency of conversion over time fits tightly with an exponential function ( $R = .99$ , see figure 1).

Appropriate approval and procedures were used concerning human subjects. Indeed, according to the Declaration of Helsinki (BMJ, 1991; 302: 1194), all participants gave their written consent to participate to the study, which was approved by the ethics committee of the University Hospital of Liège.

The experimental task was also administered to 21 healthy controls, without cognitive problems, as confirmed by a normal score on the Mattis Dementia Rating Scale (DRS [23]). They had no psychiatric problems, they were free of medication that could affect cognitive functioning, and they reported being in good health. In considering demographic and clinical data as a function of follow-up diagnosis (Table 1), the 23 stable QAD patients were younger than the 27 patients who subsequently converted to AD and the controls, and the converters scored lower on the initial Mattis DRS and the MMSE than the stable QAD subjects and the controls. In contrast, there was no difference in terms of education between the three groups. Moreover, the stable QAD subjects and the AD converters did not differ on measures of executive function such as the Stroop test [24] and a verbal fluency test.

<Table 1 about here>

## 2.2. *Experimental task*

Participants were individually submitted to the French version of a stem completion task (described in details in Adam et al. [8]). The stimuli comprised 112 six-letter French words, for which the first three letters (stem) were all different. The task comprised two separate conditions (inclusion and exclusion). Condition order was counterbalanced across participants (half of them beginning with the inclusion condition).

Each condition involved the intermixed presentation of words and stems. Each word was presented on a computer screen for 3 s. Participants were asked to read the words aloud and to try and remember them. After a word had been encoded, the first three letters of this word appeared either immediately after presentation of the word (Lag 0), after three words (Lag 3) or after 12 words (Lag 12). During the retention interval, participants had to either encode new words or complete stems related to previously encoded words. The stems stayed on the screen until the participants gave an answer or for a maximum of 15 s. Participants had to complete them following two different sets of instructions according to the condition.

In the inclusion condition, participants had to complete the stem with a word that had been presented in the list. If they did not remember any such word, they were asked to complete the stem with the first six-letter word that came to mind. In the exclusion condition, participants were asked to avoid completing the stem with a previously studied word and to give a new six-letter word beginning with the same three letters.

Before the task started, participants were also informed that it would not always be possible to recall a previously seen word for some stems, because no corresponding word had actually been presented (baseline condition). In this case, they should give the first six-letter word that came to mind. The baseline condition gave the base-rate level of completion for stems (i.e. random probability of completing the stem with the chosen target word without having seen it).

Controlled and automatic 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 complete a stem with a previously studied word because they consciously remembered it (C) or because it was the first word that came to mind automatically (A) without any recollection ( $1 - C$ ). Thus, the probability of completing a stem with a previously presented word in the inclusion condition is formalized as  $I = C + A(1 - C)$ . By contrast, in

the exclusion condition (E), participants might incorrectly complete the stem with a previously studied word because the word came automatically to mind (A) without any controlled memory of its prior appearance ( $1 - C$ ). So, the probability of completing the stem with an old word in the exclusion condition is represented by  $E = A (1 - C)$ .

Given these two equations, an estimate of controlled processes is obtained by subtracting the proportion of exclusion trials completed with an old word from the proportion of inclusion trials completed with an old word:  $C = I - E$ . An estimate of automatic processes is computed by dividing the proportion of exclusion trials completed with a previously studied word by the estimated probability of a failure of controlled processes:  $A = E / (1 - C)$ .

### *2.3. PET acquisition method*

PET images were acquired at entry only, in all patients, on a Siemens CTI 951 R 16/31 scanner during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of 110 to 370 Mbq  $^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose. Images of tracer distribution in the brain were used for analysis: scan start time was 30 min after tracer injection and scan duration was 20 min. Images were reconstructed using filtered backprojection including correction for measured attenuation and scatter using standard software.

### *2.4 Image Processing*

Using statistical parametric mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK), the PET data were subjected to an affine and non-linear spatial normalization onto the SPM5 standard PET brain template. A mean image was then generated from all the resulting normalized images and smoothed using an 8-mm full-width at half-maximum isotropic Gaussian filter. This mean image served as a brain template specific to the patient group. Each PET image was then spatially normalized onto this group-specific brain template. Finally, images were smoothed with a 12-mm full-width at half-maximum filter.

Proportional scaling was used to control for individual variation in global  $^{18}\text{F}$ FDG uptake [25], as this is the best method in a scanner with a limited field of view, where the cerebellum is cut at different levels and cannot be taken as reference structure. To test hypotheses about region-specific effects, the parameters were estimated according to the general linear model at each voxel. The statistical analyses performed in SPM5 consisted of multiple regression analyses where individual PET images were entered as independent variable for each group (AD converters and stable QAD) and with the estimates of controlled memory processes (collapsed across Lags 3 and 12 to provide a single, more sensitive measure), age and MMSE score as covariates. Age and MMSE score served as nuisance variables because they differed between AD converters and stable QAD patients. In the AD converters group, time of conversion was also included as confounding variable. In order to isolate the metabolic correlates of controlled memory processes, linear contrasts were used to identify the brain regions where metabolism was positively correlated with controlled processes in each group. Clinical magnetic resonance imaging (MRI) had already been performed in most patients before their inclusion in the study, on a variety of machines, and we did not have the possibility of performing experimental structural MRI to correct the brain metabolism for atrophy in this population.

Based on the literature on functional neuroimaging of memory, specific brain coordinates associated with controlled memory processes were selected a priori for small volume correction (SVC) on whole brain statistical maps in SPM5. Interest in those areas was motivated by publications dealing with controlled retrieval from episodic memory and related concepts, such as retrieval success (i.e., retrieval of episodic information and explicit consciousness that information is old). Peak locations (in MNI coordinates) for areas associated with controlled and successful retrieval from memory were: (1) the medial temporal lobe, including the perirhinal cortex:  $-24 -16 -36$  [26], the hippocampus:  $-15 -5 -$

25 [26], and the parahippocampal cortex: 21 –38 –14 [27]; (2) the left parietal cortex (BA 39/40): –39 –58 36 [28-29]; (3) the posterior cingulate cortex: 0 –32 37 [30]; (4) the left anterior frontal cortex (BA 10/46): –35 52 11 [28, 31]; (5) the left inferior ventrolateral frontal cortex: –45 36 –2 (BA 45/47) and –47 16 26 (BA 44) [31]; and (6) the dorsomedial prefrontal cortex: –6 34 47 (BA 8 [30, 32]).

We first searched for voxel-based correlation in the entire brain on SPM using a  $p < .05$  (FWE-corrected for multiple comparisons) and a  $p < .001$  (uncorrected). In the latter case, the SVC routine in SPM5 was subsequently used for confirmation, testing a priori hypotheses about brain coordinates of interest. Hypothesis-driven analyses were performed using a 10-mm sphere centred on the above-mentioned coordinates that corresponded to regions observed on the statistical parametric map at  $p < .001$  uncorrected. The threshold of significance was set at  $p_{SVC} < .05$  corrected for multiple comparisons.

### 3. Results

#### 3.1. Behavioral data

*3.1.1. Word stem completion.* For the AD converters, the stable QAD patients and the control group, the proportions of stems completed with the target words in the baseline condition (new items), the inclusion condition (Lags 0, 3 and 12) and the exclusion condition (Lags 0, 3 and 12) are reported in Table 2.

<Table 2 about here>

First, analyses were performed on the probability of giving the target word when completing a stem even though this target word had not been seen earlier (i.e., new items). A 3 (Group: AD converters vs. stable QAD vs. controls) by 2 (Condition: inclusion vs. exclusion) analysis of variance (ANOVA) did not reveal any significant effect (all  $ps > .31$ ).

Thus, the probability of guessing was similar in all the groups and the same criterion was used to respond in both conditions.

Second, the proportion of completion of stems presented immediately after encoding of the corresponding word (Lag 0) was examined. There was no significant difference between the groups in either condition [inclusion:  $F(2, 68) = 0.85, p > .43$ ; exclusion:  $F(2, 68) = 1.42, p > .24$ ]. Thus, the patients were able to adequately follow the instructions, and so the estimates of controlled and automatic processes can be considered to be valid.

The proportion of stems completed with the target word in the inclusion condition was then analyzed with Group (AD converters vs. stable QAD vs. controls) as between-subject variable and Lag (3 vs. 12) as within-subject variable. The results showed a main effect of Group,  $F(2, 68) = 7.82, MSE = 0.04, p < .01$ . HSD Tukey test showed that the control group produced more target words than the QAD patients, but there was no difference between the AD converters and the stable QAD. The main effect of Lag was also significant,  $F(1, 68) = 94.69, MSE = 0.01, p < .01$ . The completion score was better at Lag 3 than at Lag 12. Finally, the interaction was not significant,  $F < 1$ . In the exclusion condition, a 3 (Group) by 2 (Lag) ANOVA did not yield any significant result (all  $ps > .09$ ).

*3.1.2. Estimates of controlled and automatic processes.* The estimates of controlled and automatic processes are shown in the lowest part of Table 2. Controlled process estimates underwent a two-way ANOVA (Group  $\times$  Lag). The results revealed a main effect of Group,  $F(2, 68) = 8.93, MSE = 0.06, p < .01$ . Controlled processes were less efficient in the QAD patients than in the controls, with no difference between the two patient subgroups. There was also a main effect of Lag,  $F(1, 68) = 77.00, MSE = 0.01, p < .01$ , showing a decrease in controlled processes as the retention interval increased (3 vs. 12). The Group by Lag interaction was not significant ( $F < 1$ ). As for the estimates of automatic processes, a 3

(Group) by 2 (Lag) ANOVA showed a significant main effect of Lag,  $F(1, 68) = 5.03$ ,  $MSE = 0.01$ ,  $p < .05$ . This effect showed that automatic processes were lower at Lag 12 than at Lag 3. Automatic processes did not differ between groups, and there was no interaction ( $F_s < 1$ ).

Finally, as the women/men ratio differ between the patient group and the control group (56% of women in the patient group vs. 81% of women in the control group), the ANOVAs were also performed with gender as a between-subject variable. No difference as a function of gender was observed, and there was no significant interaction between gender and group.

### *3.1.3. Influence of the level of education on controlled and automatic processes.*

Among the AD converters, there were 20 patients with a high educational level (74%) and 7 patients with a low educational level. In the stable QAD group, there were 18 high-educated patients (78%) and 5 low-educated patients. There was no difference in the proportion of high- and low-educated patients between the groups (Chi-square = 0.12,  $p > .72$ ). Given the small number of participants in some subgroups, between-group comparisons of controlled and automatic processes estimates were performed using non-parametric Mann-Whitney tests. The comparison of high-educated and low-educated patients in each group (converters and stable QAD) failed to reveal any significant difference on controlled and automatic estimates (all  $p_s > .14$ ). When the performance of each subgroup was compared with that of controls with the same educational level (4 controls with a low educational level and 17 controls with a high educational level), both the converters and the stable QAD with high educational level showed deficient controlled memory processes,  $Z = -3.7$  and  $-1.9$  respectively,  $p < .05$ , but preserved automatic memory processes,  $Z = 0.09$  and  $0.08$  respectively,  $p > .92$ . The comparison of converters and stable QAD with low educational level ( $n=5$ ) versus controls ( $n=4$ ) failed to reach significance for controlled estimates,  $Z = -1.6$ ,  $p < .11$ , and was not

significant for automatic estimates,  $Z = -0.2$  and  $0.8$  respectively,  $p > .39$ . However, given the very small number of participants included and the absence of difference in other comparisons, it certainly is hazardous to conclude that low-educated patients had preserved controlled memory processes.

### 3.2. Metabolic data

*Metabolic comparisons between converters and stable QAD.* This comparison was performed in SPM5 taking age and MMSE score as confounding covariates. Patients who subsequently converted to Alzheimer type dementia showed significantly decreased brain metabolism at baseline compared to stable QAD ( $p < .001$  uncorrected) in the left precuneus, the right inferior parietal lobule and bilateral middle temporal cortex. Such a distribution of impaired metabolism in associative cortices is classically observed in neuroimaging studies of AD patients [33-34],

#### *Cognitive and metabolic correlations.*

Voxel-based correlations were computed ( $p < .05$  FWE-corrected and  $p < .001$  uncorrected) for the AD converters and the stable QAD groups and SVC was further applied in specific brain coordinates associated with controlled and successful retrieval of information from episodic memory ( $p_{SVC}$  FWE-corrected, voxel-level  $< .05$ ).

When looking at the metabolic correlates of controlled memory processes at entry in the 27 patients who subsequently converted to AD (during the 36-month follow-up period), significant positive correlations were found in the right dorsal posterior cingulate cortex (~ BA 31, MNI coordinates  $x = 4$   $y = -34$   $z = 38$ ,  $p_{SVC}$  corrected  $< .05$ ) and the dorsomedial prefrontal cortex (~ BA 8, MNI coordinates  $x = 2$   $y = 36$   $z = 48$ ,  $p$  corrected for the entire brain  $< .05$ ; see Figure 2). This suggests that decreased activity in those dorsomedial and

posteromedial regions is related to poorer controlled memory performances in very early AD patients.

In the 23 QAD patients who remained stable, lower scores of controlled memory processes were correlated with decreased metabolic activity in the left anterior medial temporal lobe (MTL), encompassing the hippocampus and the entorhinal cortex (MNI coordinates  $x = -20$   $y = -6$   $z = -24$ ,  $pSVC$  corrected  $< .05$ , see Figure 3).

<Figures 2 and 3 about here>

#### 4. Discussion

This study aimed at examining the neural basis of controlled memory processes in the early stages of Alzheimer's disease. Controlled and automatic uses of memory were isolated by means of the Process Dissociation Procedure and examined in a group of 50 QAD patients. After a follow-up period of 36 months, it was possible to compare the patients retrospectively as a function of the clinical outcome at the last neuropsychological testing (AD or stable QAD). The metabolic correlates of controlled memory processes in each subgroup were explored via FDG-PET images.

The main behavioural findings were that QAD patients showed impaired controlled memory processes, but preserved automatic processes. Moreover, the patients who subsequently converted to AD and those who remained stable could not be distinguished in terms of the severity of their controlled memory deficit at entry in the study. However, voxel-based cognitive and metabolic correlations suggested that the cerebral regions preferentially associated with controlled memory processes differed in the AD converters and the stable QAD patients.

At a clinical level, the follow-up of the patients with a neuropsychological battery confirmed that the diagnosis of QAD (or MCI) incorporates qualitatively different patients

[16, 21]. It should be noted that the 50 patients analyzed in the study came from an original group of 59 QAD patients. Among the 9 patients who were not included in the analyses, five patients did not complete the follow-up, two converted to frontotemporal dementia, one returned to the normal level and one was diagnosed with depression. Approximately 45% of the initial group progressed to AD in 3 years. This conversion rate is similar to what has previously been reported for follow-up periods of 36 to 48 months [35-36]. Interestingly, most conversions to AD occurred within one year after entry into the study. Moreover, multiple-domain aMCI patients seemed to progressed to AD at a higher rate and earlier than single-domain aMCI patients, as previously reported [37]. A high level of education is known to delay the onset of Alzheimer's disease in community-based elderly people (e.g. [19]), but little is known on its influence on conversion in QAD populations. In the current study, there was no difference related to educational level between converters and stable QAD. It should be noted however that most patients were highly educated, and all but one passed the primary school diploma. Letenneur et al. [19] showed that the critical educational threshold is the achievement of the primary school diploma, as people who reached this threshold have a lower risk, independently of the number of years of education they completed afterwards. As almost all patients could be considered as high-education with regard to Letenneur et al.'s categorization, differences in educational level probably had a very limited impact, if any, on the progression to dementia in our sample.

#### *4.1. Memory performances*

At the behavioural level, QAD patients were characterized by a dissociation between impaired controlled memory processes and intact automatic processes. Even after the shortest retention interval (three intervening items), the patients found it difficult to consciously recall the previous occurrence of studied words. In contrast, when they failed to explicitly recall the

studied word, the previous encounter with this word nevertheless influenced (primed) their response to the stem. So priming seems to be intact in QAD patients, at least when assessed by a word stem completion paradigm and when one uses a procedure that avoids contamination of implicit memory by explicit retrieval. This result extends to patients with QAD the dissociation between controlled and automatic processes previously observed in AD [8].

It is noteworthy that scores for controlled memory processes could not distinguish the patients who would develop dementia in the following 36 months from those who would not. At first sight, this finding somewhat contrasts with the idea that a deficit affecting controlled aspects of cognition represents an early indicator of dementia [4]. However, Fabrigoule et al. distinguished future converters from future normal participants, whereas our study compared two subgroups of cognitively impaired elderly participants. Thus, one could argue that stable QAD patients may eventually convert to AD later on. Moreover, we focused on the memory domain, while Fabrigoule et al. examined a general cognitive factor that incorporates controlled aspects of a variety of tasks. Actually, our results suggest that even if a deficit affecting particularly the controlled aspects of memory function is sensitive to early dementia, it may not be specific. In fact, such a deficit has been described in a number of other pathologies, such as depression [38], chronic pain [39] and hippocampal amnesia [40-41].

#### *4.2. Neural correlates of controlled processes in pre-dementia stages of Alzheimer's disease*

Although the neural correlates of episodic memory were previously searched for in the AD literature [9-10, 42-48], previous studies did not specifically assess controlled memory retrieval uncontaminated by automatic processes. Among the AD converters, we found that the poorer the controlled memory performance for cued retrieval, the lower the metabolism in the posterior cingulate cortex and in the dorsomedial prefrontal cortex (BA 8). Thus, whereas

important lesions of the medial temporal lobe are present very early in AD [13] and have sometimes been related to AD patients' impaired retrieval of information from episodic memory (e.g., Lekeu et al. [46]), the present study indicates that the deficit affecting controlled processes in episodic memory cannot be reduced to the prominent pathology of the hippocampal formation but is associated with a dysfunction of anterior and posterior medial cortical regions. This is also consistent with evidence that a relative dysfunction, at a pre-dementia stage, of medial frontal regions and posterior cingulate cortex is characteristic of future AD patients [33-34, 49-51].

An association between controlled memory processes and the dorsomedial prefrontal cortex has been previously reported in the neuroimaging literature [52]. Activation of a nearby region has been reported in several fMRI studies of episodic memory, particularly when participants successfully recollected contextual information (during source or contextual memory [32, 53-54] or for Remember versus Know responses [30]). Interestingly, a recent study showed that, in patients with mild AD, the proportion of correctly recollected words (as measured by Remember responses) correlated with metabolism in the frontal regions, including a dorsomedial prefrontal region very close to the one reported here [55]. The dorsomedial prefrontal cortex was also activated when normal participants elaborated on episodic memories and possible future episodic events [56]. Finally, in a PET study, D'Argembeau et al. [57] reported that the dorsomedial prefrontal cortex increased its activity when participants engaged in reflection about themselves, another person or society in contrast to at rest. They suggested that this region may play a role in the monitoring of personal or other persons' states or characteristics (e.g., considering one's own internal experience or understanding other people's mental states). Together, these neuroimaging data suggest that the dorsomedial prefrontal cortex plays a role in controlled memory processes as they relate to reflective and monitoring processes. These processes may be useful for

monitoring the products of retrieval (including associated contextual information) and deciding whether the word generated in response to the stem has actually been studied.

The finding that the metabolic activity of the posterior cingulate cortex was positively correlated with successful use of controlled memory processes in the AD converters is in keeping with previous studies showing an involvement of this region in episodic memory performance of QAD patients [25, 58-60]. For example, Chételat et al. [25] found a relationship between verbal free recall performance in QAD and posterior cingulate glucose metabolism. Also, fMRI studies showed that MCI subjects activated the posterior cingulate cortex less than control participants during episodic memory retrieval [58, 60]. Moreover, the region found here corresponds to the locus of the posterior cingulate regions activated by recollection more than familiarity [30, 61], and by successful source retrieval [62]. Thus, the posterior cingulate cortex may play a role in the reactivation of previously encoded episodes.

#### *4.3. Neural correlates of controlled processes in stable QAD*

In the stable QAD patients, more efficient controlled memory processes were associated with higher metabolic activity in the anterior part of the left MTL, encompassing the hippocampus and entorhinal cortex. Previous imaging studies in healthy participants and in early AD suggested that the anterior hippocampal formation plays a role in reactivating associations created at encoding, allowing subjects to recollect the contextual details linked to items [26, 43, 63-64]. The possibility that the left anterior medial temporal area is involved in associative retrieval is compatible with the demands of the present task, which consisted of cued recall in which a stem must reactivate an old word and potentially its associated context at encoding.

It should be considered that the anterior part of the parahippocampal region has also been associated with familiarity-based retrieval, that is, the feeling that a piece of information

is old without any recollection of the context of encoding [65]. One cannot exclude a contribution of familiarity in the present task, because, in presence of a stem, a previously seen word may come automatically to mind and then be consciously judged as old because it feels familiar to the participant, although there is no recollection of contextual details. However, in fMRI studies of retrieval processes, familiarity is associated with deactivation, rather than activation, of the anterior medial temporal lobe. Yet, in the present study, a positive association was observed between anterior hippocampal/entorhinal metabolic activity and higher controlled memory performance.

#### *4.4. Heterogeneity of metabolic correlations in QAD*

The current findings of different brain correlates of controlled memory processes in AD converters and stable QAD may be interpreted in light of the dynamical brain changes over the course of mild cognitive impairment and early Alzheimer's disease. Early in the course of mild cognitive impairment, when dysfunction of the hippocampus and entorhinal cortex is still minimal, hyperactivation of the medial temporal lobe can be seen during a memory task performed in an fMRI scanner [66-68]. Regional cerebral blood flow measured with continuous arterial spin-labeling magnetic resonance imaging has also been found to be increased in the hippocampus and amygdala in MCI patients [69]. Increased activation/activity of the MTL may indicate that compensatory mechanisms are at work [69-70]. Such compensatory processes may explain the relationship between MTL activity and controlled processes in some stable QAD patients. Indeed, patients with the highest MTL metabolism demonstrated better use of controlled memory processes. Hence, the stable QAD patients are at a sufficiently early stage, so that MTL activity can still support controlled memory processes.

When patients enter a more advanced stage of mild cognitive impairment, that follow-up revealed to be a very early AD stage, the medial temporal structures may be so damaged that they can no longer support memory processes, and then controlled memory processes are preferentially associated with other brain regions. In the present group of very early AD patients, controlled memory processes correlated with activity in the dorsomedial prefrontal and posterior cingulate cortices. This is consistent with the idea that MTL atrophy leads to some reorganization in brain functioning at the MCI stage of Alzheimer's disease. For instance, in QAD, the volume of right hippocampus and entorhinal cortex correlated negatively with perfusion in the medial and dorsolateral prefrontal cortex [71]. Increased perfusion of the prefrontal cortex has also been found in MCI who converted to AD within 2 years compared to controls and non-converters [72]. The results suggest that even at a very early AD stage, the MTL was too damaged to support memory processes and the much variable activity in dorsomedial prefrontal and posterior cingulate cortex was preferentially responsible for the variability in controlling the retrieval of information from episodic verbal memory.

Finally, it should be noted that the correlational approach used here underlined the existence of a continuum in the neuropsychological deficit demonstrated by the patients as well as in their functional brain damage. The analyses revealed that, within this functional continuum, there are two nodes, the variable activity of which was more particularly associated with controlled memory processing: on the one hand, the medial temporal lobe in stable QAD patients, and on the other hand, the posterior cingulate/dorsomedial prefrontal regions in very early AD patients when damage to the MTL do no longer support individual performance in controlled processes.

#### *4.5. Potential models of the neural correlates of controlled memory processes in dementia*

It is interesting to note that the regions found to correlate with controlled memory processes in pre-dementia AD patients and stable QAD patients belong to the default network, a network of intrinsically correlated regions that activates during free-thinking in resting state and internally-focused tasks [73-74]. The regions belong also to the core network which is involved in retrieving previous events and imagining future ones [56, 75]. Previous studies have shown a disruption of the default network in Alzheimer's disease and mild cognitive impairment [76-82] and suggested a link with the memory deficit observed in the patients. The current data suggest that, within the default or core network, whose general function may be mental simulation or anticipating the future, the medial prefrontal cortex, the posterior cingulate cortex and the hippocampal formation are more specifically concerned with the controlled access to memory representations of personally experienced events. Recently, Jaffard et al. [83] proposed that, within the default network, the medial prefrontal cortex and the posterior cingulate cortex have a role in top-down inhibitory control, which serves to refrain from reacting automatically to events. Our results thus join them in relating these regions to the concept of controlled processes (see also Vincent et al., 2008).

A concept closely related to that of control is consciousness. Although the distinctions conscious/unconscious and controlled/automatic are not interchangeable (i.e. controlled processes are not always conscious [84-85]), Jacoby argued that the Process Dissociation Procedure applied to word stem completion distinguishes controlled and conscious reactivation of a memory trace from automatic and unconscious influence of memory on performance [14]. From this point of view, the current data can be related to the neuronal global workspace for conscious processing of information [86-88]. In this model, the neuronal global workspace constitutes a distributed neural system interconnected to distant cortical and subcortical processors specialized in the non-conscious processing of specific type of information. Via top-down mobilization, the neuronal global workspace can amplify

information from a processor and make it experienced consciously and available to various processes, including memory, evaluation and verbal reports. In AD, the decrease in controlled processes of memories associated with a dysfunction of the medial frontal and posterior regions may represent an aspect of the dysfunction of the neuronal global workspace for conscious processing of information.

However, relating the neural correlates of controlled memory processes as measured by the Process Dissociation Procedure to theoretical models of consciousness is complicated by the ambiguous relationship between the concepts of consciousness and controlled processes. Moors [84] has proposed specific definitions of each concept. Thus, controlled processes refer to processes for which one has a goal (to engage the process or to stop it) and which end with the achievement of the desired effect. In contrast, consciousness refers to the availability of some content to a subjective feeling. In the present task, controlled completion of the stems with a studied word also involved awareness of its status as an old item. So the task did not allow assessing orthogonally controlled processes and consciousness. Formally, it is the distinction controlled/automatic that is put forward here, and the results suggest that, in very early AD, the dorsomedial prefrontal cortex and the posterior cingulate cortex are associated to top-down control over memory production.

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Table 1.

Demographic and clinical data as a function of follow-up diagnosis

	AD converters	Stable QAD	Controls
Age	72.0 (5.9)*	67.1 (8.6)	71.7 (5.1)
Women/men	16/11	12/11	17/4
Education (years)	11.1 (3.8)	12.0 (4.2)	11.2 (3.05)
MMSE	25.5 (2.0)*	27.1 (1.6)	–
Mattis DRS <sup>a</sup>	131.5 (6.8)*	137.6 (5.2)	139.4 (2.3)
Stroop <sup>b</sup>	129.2 (82.8)	99.5 (58.3)	–
Verbal fluency <sup>c</sup>			
Phonological	18.6 (8.7)	18.3 (7.7)	–
Semantic	20.7 (6.3)	24.3 (8.4)	–

Note: Standard deviations appear in parentheses.

<sup>a</sup> Score available for 21 stable QAD patients, 23 AD converters and 20 controls.

<sup>b</sup> Time in seconds for interference condition minus time for naming condition.

<sup>c</sup> Number of words produced in 2 min, for letter P (phonological) and animals (semantic).

\* Significant difference between groups,  $p < .05$ .

Table 2.

Proportions of stems completed with target words as a function of condition (Inclusion versus Exclusion) and item type (new, Lag 0, Lag 3, Lag 12), and estimation of controlled and automatic processes in AD converters, stable QAD and controls.

	AD converters		Stable QAD		Controls	
Inclusion New	.09 (.08)		.10 (.07)		.12 (.08)	
Exclusion New	.10 (.06)		.12 (.08)		.09 (.06)	
Inclusion Lag 0	.82 (.18)		.87 (.16)		.87 (.12)	
Exclusion Lag 0	.05 (.08)		.06 (.10)		.02 (.04)	
	Lag 3	Lag 12	Lag 3	Lag 12	Lag 3	Lag 12
Inclusion	.51 (.16)	.34 (.11)	.55 (.18)	.36 (.24)	.68 (.13)	.48 (.14)
Exclusion	.21 (.11)	.24 (.13)	.19 (.15)	.19 (.11)	.15 (.06)	.18 (.11)
Estimates of controlled processes	.30 (.20)	.10 (.19)	.36 (.22)	.20 (.27)	.54 (.14)	.30 (.18)
Estimates of automatic processes	.29 (.13)	.25 (.11)	.28 (.18)	.25 (.14)	.33 (.18)	.25 (.12)

Note: Standard deviations appear in parentheses.

Figure Legends

Figure 1. Exponential conversion to AD over time in the AD converters group.

Figure 2. Results of SPM5 analysis in the QAD patients who subsequently converted to AD: Positive correlation between metabolic activity of the dorsomedial prefrontal cortex and right posterior cingulate cortex and controlled memory processes (C) in the AD converters is displayed on a T1-weighted MRI, and the corresponding design matrix is shown.

Figure 3. Results of SPM5 analysis in the stable QAD patients: Positive correlation between metabolic activity of the left anterior medial temporal lobe and controlled memory processes (C) in the stable QAD is displayed on a T1-weighted MRI, and the design matrix is shown.

Figure 1

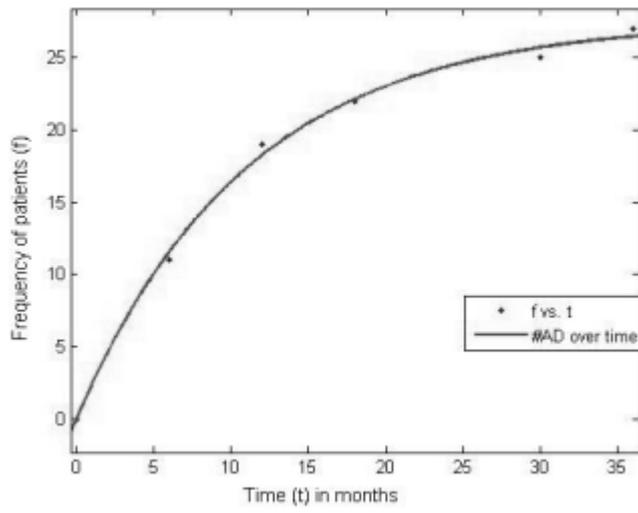


Figure 2

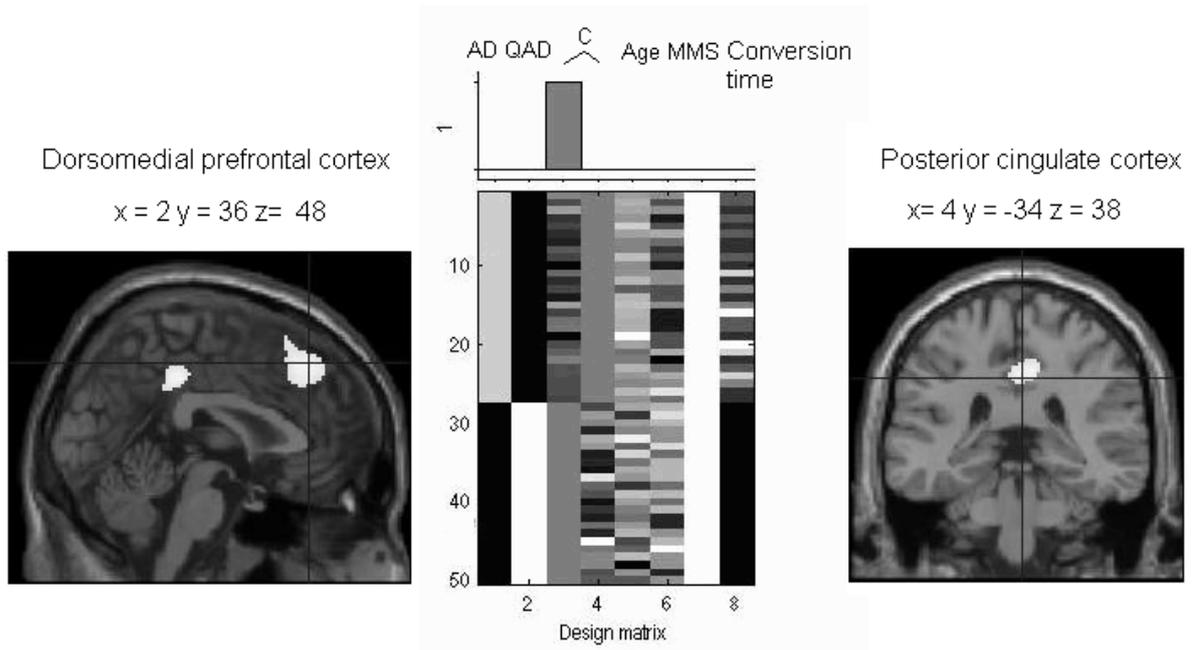


Figure 3

