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Exploring the Domain Specificity and the Neural Correlates of Memory Unawareness in Alzheimer's disease

Lucile Meunier-Duperray^{1,2}, Céline Souchay¹, Lucie Angel², Eric Salmon³, Christine Bastin³

¹ Univ. Grenoble Alpes, Univ. Savoie Mont Blanc, CNRS, LPNC, 38000 Grenoble, France,

² Université de Tours, Université de Poitiers, UMR CNRS 7295 Centre de Recherches sur la Cognition
et l'Apprentissage, Tours, France

³ GIGA-Cyclotron Research Center-in vivo Imaging, University of Liège, Liège, Belgium

Corresponding Authors:

Lucile Meunier-Duperray

Lucile.meunier-duperray@univ-grenoble-alpes.fr

Laboratoire de Psychologie & NeuroCognition (LPNC CNRS 5105)

Université Grenoble Alpes

1251 avenue Centrale Domaine Universitaire de St Martin d'Hères

38040 Grenoble France

Christine Bastin

Christine.Bastin@uliege.be

CHU - B34

Quartier Hôpital

Avenue de l'Hôpital, 11

4000 Liège, Belgium

Abbreviations

AD	Alzheimer's disease
CAM	Cognitive Awareness Model
DMN	Default Mode Network
FOK	Feeling-of-knowing
MARS	Memory Awareness Rating Scale
MCI	Mild Cognitive Impairment
MDRS	Mattis Dementia Rating Scale
MMSE	Mini Mental State Examination
ROI	Regions of interest

Abstract

Patients with Alzheimer's disease are less accurate than controls to predict their episodic performance, but they are as accurate as controls to predict their semantic performance. However, the dissociation between episodic and semantic metamemory had never been tested directly in the same patients. This study aimed to explore the dissociation between episodic and semantic metamemory in Alzheimer's disease using the feeling-of-knowing paradigm. In addition, we investigated the link between memory awareness and resting-state cerebral glucose metabolism and gray matter density, in episodic and semantic tasks independently. Data from 50 patients with Alzheimer's disease were compared to data from 30 healthy controls. Results showed that patients with Alzheimer's disease had more difficulties to predict their recognition in the episodic task than in the semantic task, while this difference was smaller in controls. Lack of awareness in the episodic task was associated with hypometabolism in right frontoparietal areas in patients with AD. These results support the idea of a dissociation between episodic and semantic metamemory in Alzheimer's disease.

Keywords. Alzheimer's disease, feeling-of-knowing judgments, metamemory, neural correlates

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1. Introduction

Patients with Alzheimer's disease (AD) are often unaware of the importance of their cognitive deficits (Clare et al., 2010; Ernst et al., 2015; Morris & Mograbi, 2013; Ries et al., 2012), and this lack of awareness is called *anosognosia* (Babinski, 1914). Anosognosia in AD has been largely explored in the field of metacognition (see Moulin, 2002 for a review). This term refers to the ability to monitor and regulate cognitive performance (Flavell, 1976). Several metacognitive processes seem to be impaired in AD, but the dissociations observed between different cognitive domains are not clearly defined (see Souchay, 2007 for a review). The aim of this study was to explore the domain specificity of memory awareness in AD and the associated neural correlates.

The cognitive awareness model (CAM) was developed to identify the different processes of awareness and define the role of memory in anosognosia (Agnew & Morris, 1998; Morris & Mograbi, 2013). According to this model, a comparator mechanism compares current performance with expected performance. Expected performance is built on information from a personal database, which stores semantic representations of personal abilities. In the event of a mismatch between actual and expected performance, the personal database can be updated. For instance, let's imagine two elderly people who are looking for their glasses but cannot find them. For the first person, the episodic information "I thought that I let my glasses here" is compared with the semantic representation "I usually lose my glasses", and the personal database is not updated. For the second person, the same episodic information can be compared

with the semantic representation “I usually do not lose my stuff”, and the personal database can be updated: “my memory is not as good as it used to be”.

Anosognosia can be assessed using discrepancy scores between patients’ ratings and those of their relatives (e.g., the Memory Awareness Rating Scale, also called MARS; Clare et al., 2010). The items of the MARS are based on everyday situations that involve memory (e.g., capacity to find their car in a parking lot). Using this method, patients with AD frequently overestimate their memory performance, but some patients underestimate it (Antoine et al., 2019; Clare et al., 2010). Patients’ ratings are not correlated with those of their relatives, suggesting a lack of memory awareness in AD (Ries et al., 2012). Nevertheless, these types of questionnaires are largely dependent on representations, knowledge, beliefs, normative expectations, and subjective experience of the disease and aging (Clare et al., 2011; Cosentino et al., 2015; Kaszniak & Zak, 1996).

Additionally, memory awareness has been explored using objective tools derived from the experimental method of the metamemory field, such as the feeling-of-knowing paradigm (FOK paradigm). This paradigm consists of three phases (Hart, 1965). Firstly, a recall phase presents cues to participants (e.g., definitions, questions, words). Participants have to retrieve the target associated with the cue. Secondly, participants provide a FOK judgment whereby they have to judge if they could recognize the right target among several propositions. Thirdly, they proceed to the recognition phase. Participants have to recognize the right target presented with several distractors. The FOK paradigm can be performed with episodic material in which cue-target associations have been studied prior to the cued-recall phase (e.g., word pairs; Schacter, 1983), or semantic material in which the target refers to information stored in semantic memory (e.g., vocabulary, general knowledge; Hart, 1965).

The accuracy of FOK judgments is assessed by combining memory performance and FOK judgments. Thus, FOK accuracy could be defined as the ability to adapt judgments according to memory performance. Patients with AD are less accurate than controls in episodic FOK tasks, but they are as accurate as healthy elderly adults in semantic FOK tasks (see Souchay, 2007 for a review). Nevertheless, no study has ever directly compared FOK accuracy between episodic and semantic tasks in patients with AD, making it impossible to conclude that a true dissociation exists.

The patient' difficulties in making accurate judgments in episodic FOK tasks could result from poorer use of memory cues. Episodic FOK accuracy is based on recollection of temporospatial cues, as well as on autoegetic consciousness, which refers to the very personal feeling of remembering (Souchay et al., 2007). The subjective experience of retrieval can be explored using the Remember/Know procedure. Participants are asked to indicate whether they *Remember* (i.e., recollect spatiotemporal information about the target, such as mood, semantic features, thoughts, etc.) or *Know* (i.e, feeling of familiarity, without retrieving details) the response during a recognition phase of an episodic task. Using this procedure, patients with AD produce fewer Remember responses than controls, while they give the same number, or sometimes more Know responses than controls (Barba, 1997; Rauchs et al., 2007). It is therefore proposed that recollection cues of patients with AD are less rich than those of healthy controls (Souchay & Moulin, 2009). This raises the question of whether the episodic FOK deficit in AD could result from patients' difficulties in using recollection during metamemory judgments.

In healthy adults, higher FOK judgments are linked to a greater activity in the medial parietal, fusiform, right superior temporal, and hippocampal regions (Chua et al., 2009). These activations depend on the nature of the task with greater activation of the ventral region of

posterior parietal cortex during episodic than semantic FOK judgments, and activation of the anterior temporal region during semantic FOK judgments (Elman et al., 2012). In AD, metamemory performance seems to be negatively correlated with the gray matter volume of the right medial prefrontal cortex and of the right posterior cingulate cortex (Bertrand et al., 2018; Genon et al., 2016; Hallam et al., 2020), but the neural correlates of episodic and semantic metamemory independently are still unclear.

Cerebral regions frequently associated with anosognosia in AD include (among others) the inferior frontal gyrus, anterior and posterior cingulate cortex, and medial temporal lobe (Hallam et al., 2020; Mondragon et al., 2019; Salmon et al., 2024). Furthermore, anosognosia appears to be associated with frontal lobe damage (Ernst et al., 2015; Kaszniak & Zak, 1996; Ries et al., 2012). It has been proposed that executive decline linked to the frontal lobe damage observed in AD participate to the lack of awareness (Clare et al., 2011; Ernst et al., 2015; Morris & Mograbi, 2013).

In summary, behavioral and neuroimaging results showed that memory awareness in AD seems to differ between episodic and semantic tasks. Nevertheless, no study has ever directly compared episodic and semantic FOK judgments in patients with AD, making it impossible to conclude that this dissociation exists. This study had two main aims: (1) First, we tested for the dissociation between episodic and semantic FOK performance in AD. We expected patients to be less accurate than elderly controls when asked to judge their memory performance in the FOK task. Given that previous studies showed a metamemory deficit in AD with episodic tasks but not with semantic tasks (Souchay, 2007), we hypothesized that metamemory performance in patients with AD should be poorer in the episodic task than in the semantic task, while this difference would not be observed in controls. (2) Second, we expected that metamemory

performance would be related to glucose metabolism and gray matter integrity in frontal regions. Moreover, the episodic FOK task would be related to posterior parietal regions.

For exploratory purposes (hypotheses not preregistered), we explored the subjective state of remembering using the Remember/Know procedure. Given the recollection deficit, patients with AD should produce fewer Remember responses and more Know responses than controls. If there is an episodic FOK deficit in AD, we hypothesized that it is related to a deficit in partial reactivation of contextual information (Souchay et al., 2007). We expected to observe a correlation between the metamemory scores from the episodic FOK paradigm and the proportion of Remember responses. Furthermore, we hypothesized that the proportion of Remember and Know responses would be related to different regional changes in resting-state brain metabolism (FDG-PET) and gray matter integrity (structural MRI) in AD.

2. Method

2.1. Participants

Fifty patients with probable AD (32 females) and 30 healthy elderly controls (20 females) took part in the experiment. All were native French speakers. Control participants had no psychiatric or neurological antecedents, no anxiolytic or antidepressant medication, no excessive consumption of alcohol, and had normal or corrected hearing and vision. For probable patients with AD, the clinical diagnosis followed the NIA-AA criteria (McKhann et al., 2011) for typical probable AD (i.e., prominent memory difficulties) and was based on a neurological examination, neuropsychological testing, and the presence of biomarkers in FDG-PET (e.g., hypometabolism in parieto-temporal and posterior cingulate cortex; Herholz et al., 2002). The

University Hospital ethics committee approved the study (IRB #2004/172) and all participants gave their informed consent to take part in the experiment.

There were no differences between patients and controls in terms of gender, $X^2(1) = 0.01, p = .84$. However, patients with AD were older ($mean = 77.20, sd = 6.85$) than controls ($mean = 72.90, sd = 6.95$), $t(54.95) = 2.71, p < .01$. They were also less educated ($mean = 10.10$ years at school, $sd = 3.06$) than controls ($mean = 12.30, sd = 3.12$), $t(56.01) = -3.25, p < .01$. Thus, analyses of this study took age and education into account as covariates.

2.2. Neuropsychological Assessment

All participants completed a neuropsychological assessment to assess the cognitive status at inclusion of the two groups (patients with AD or controls). Patients with AD have been tested with the Mini Mental State Examination (MMSE; Folstein, 1975). In addition, all participants have been tested on the Mattis Dementia Rating Scale (MDRS; Mattis, 1976). These tests were administered in the week before or after the neuroimaging. As expected, the MMSE scores of patients with AD were below the pathological threshold ($mean = 22.60, sd = 2.90$) and their MDRS scores were lower ($mean = 118, sd = 11.30$) than those of controls ($mean = 138, sd = 5.96$), $z = -6.51, p < .001, r = 0.75$, suggesting the general cognitive impairment of patients with AD. A follow-up testing was done 5 years later in controls, participants who were still cognitively healthy during this follow-up were included in the current analysis ($n = 29$). One control participant demonstrated cognitive decline compatible with a risk of dementia and was excluded from the analyses.

2.3. The Feeling-of-Knowing paradigm

All participants performed a feeling-of-knowing (FOK) paradigm in an episodic and a semantic task. The presentation order of the two tasks was counterbalanced between participants. The procedure was adapted from Souchay and collaborators (2007). To make the task more feasible for patients with AD, two lists of items were created from the princeps article. Thus, there were 20 trials per task (instead of 40 trials in Souchay et al., 2007). The two lists of items were counterbalanced between participants and tasks. Consequently, for two different participants, an item could be a target word in either the episodic or semantic task. This allows the use of the same items in the semantic and episodic task to reduce the material effect.

The episodic FOK task began with an encoding phase during which participants saw 20 semantically related cue-target word pairs (e.g., nuclear-ELECTRON). The pairs were presented at the center of a computer screen during 5 s. The cue words were printed in lower case at the top, and the target words in uppercase at the bottom. In a cued-recall phase, participants saw cue words one by one on the computer screen (e.g., nuclear) and had 15 s to recall the target word associated with the cue. Whether or not the target was recalled, participants had 5 s to make the FOK predictions. For this, they could answer “yes” if they thought that they would recognize the target word later, or “no” if they thought that they would not recognize the target word. The recognition phase began at the end of the FOK phase. Participants had to recognize the target words in five-alternative forced choice test trials without time limit. Distractors were semantically related words (e.g., neutron, ion, proton, nucleon). After each of their responses, participants performed a Remember/Know judgment. Remember responses correspond to the recollection of specific information about the encoding context (temporal information, thoughts, memory strategies, etc.). A justification was asked for

each Remember response. Know responses correspond to a recognition without recollection of encoding context. Participants could also say that they guessed the responses.

In the semantic FOK task, participants saw 20 definitions one at a time on a computer screen (e.g., constituent element of the atom opposite the nucleus). They had 15 s to recall the word that corresponded to the definition. For each trial, participants had 5 s to make the FOK predictions with a yes/no judgment to indicate whether they would be able to recognize the word corresponding to the definition in a subsequent recognition test. Then, participants were shown again all the definitions one by one on the computer screen and they had to choose the word that best matches the definition among five alternatives, with distractors being semantic associates of the target word. They had no time limit to make their response.

2.4. Neuroimaging data Acquisition and Preprocessing

Some participants were unable to perform the structural MRI due to metal implants, and others did not consent to perform the FDG-PET, which explains the difference in the number of participants between analyses.

2.4.1. Brain metabolic measure

Cerebral glucose metabolism was measured with FDG-PET in 32 patients with AD and 23 controls. Images were acquired on a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution and 2.4 mm slice interval). Scans were acquired thirty minutes after intravenous injection of 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG, 152 to 290 MBq) (Lemaire et al., 2002). Participants were asked to stay quiet and awake with eyes closed throughout the acquisition (for 20 min). Images were reconstructed using filtered backprojection, including correction for measured attenuation and

scatter using standard software. FDG-PET image analyses were performed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). To normalize PET images, we first applied an affine and non-linear spatial normalization of each image to the PET brain template. Based on these normalized images, we generated a mean image and smoothed it using an 8-mm full-width at half-maximum isotropic Gaussian filter. Then, this average and smooth image was used as a brain template adapted from and for the sample. Finally, original PET images were spatially normalized onto this brain template and smoothed with a 12-mm full-width at half-maximum filter.

2.4.2. Structural MRI Acquisition

Structural MRI was performed in 43 patients with AD and 25 controls. A high-resolution T1-weighted image (3D MDEFT) was acquired on a 3T Siemens Allegra scanner using the following parameters: TR/TE/TI = 7.92/2.4/910 ms, FA = 15°, FOV = 256 × 240 × 176 mm², 1 mm isotropic spatial resolution (Deichmann et al., 2004). The VBM toolbox in SPM was used to extract normalized modulated images of gray matter density using default parameters. The gray matter density images were smoothed with an 8-mm full-width at half-maximum gaussian filter. A mask for gray matter was generated from the mean images of the sample and used as an explicit mask in the statistical analyses.

2.5. Measures and Statistical Analyses

A preregistration of hypotheses and statistical analyses is available on the Open Science Framework website (see Meunier et al., 2023). Given the difference in age and level of education between patients with AD and controls, these two variables were considered as covariates in both behavioral and neuroimaging analyses.

2.5.1. Behavioral data and exclusions

Memory performance was compared between patients with AD and controls with recall and recognition performance. Cued-recall performance was estimated using the proportion of correct recall. Given the non-normal distribution of the data, a Kruskal-Wallis test was performed to compare patients with AD and controls in the episodic and semantic task independently. Recognition memory was estimated with a sensitivity index (d') based on the proportion of correct responses and false alarms. To avoid infinite values from participants that recognized all items, we convert the proportion of 1 to 0.095 (Macmillan & Creelman, 2004). Participants with higher d' are better able to discriminate between targets and distractors. Given the violation of the homogeneity of variance assumption, we performed a robust mixed ANOVA using the WRS2 R package with groups as between-subjects factor (i.e., patients and controls) and tasks as within-subjects factor (i.e., episodic and semantic).

Metamemory performance was estimated through two measures: the rate of congruent responses between FOK judgment and memory performance and a measure of metamemory sensitivity (AUROC2). The rate of congruent responses was measured by the proportion of hits in the recognition phase for Yes FOK judgments (see Bastin et al., 2021). Metacognitive bias was controlled by checking the total number of Yes responses in the two groups. A second measure, based on signal detection theory, was processed to estimate the metacognitive accuracy: the AUROC2 (see Fleming & Lau, 2014). This has been calculated on the non-recalled trials (i.e., omissions). The analysis of receiver operating characteristics (ROC) assesses both type 1 (i.e., related to the task) and type 2 (i.e., related to the judgment) sensitivity (Galvin et al., 2003). To consider metacognitive bias, the responses are categorized depending on the accuracy of the answer (hit or false alarm) and on the judgment given (“yes” or “no”). The proportion of each type of response can be plotted on a ROC curve considering each

judgment criteria for both correct and incorrect responses. Metacognitive sensitivity is estimated by the area under the curve (called AUROC2; Fleming & Lau, 2014). Higher area under ROC suggests higher metacognitive sensitivity. The rate of congruent responses and the AUROC2 scores have been analyzed independently using mixed ANOVA with group as between factor (i.e., patients and controls) and task as within factor (i.e., episodic and semantic), with age and education level as covariates.

For the Remember/Know procedure, and since we did not assume the same variance in both groups, we performed a Welch *t*-test on Remember and Know responses independently. The proportion of Guess responses was not considered. To explore the link between recollective experience and metamemory, we performed correlations between the proportion of Remember responses and the two metamemory indices (i.e., congruency and AUROC2).

In all analyses, outliers were identified with boxplot methods (with the *rstatix* package on R). Participants were considered extreme when their scores were above the third quartile plus three times the interquartile range. The AUROC2 score of one patient with AD was considered as extreme in the semantic task and was removed from the AUROC2 analysis. All analyses were performed using a threshold $\alpha = 0.05$.

2.5.2. *Brain metabolic measure*

All analyses were performed on SPM12 and estimated parameters according to the general linear model at each voxel. In order to control for individual variation in global FDG uptake, a cluster of preserved activity in the patients situated in the sensorimotor area allowed to proportionally scale PET images. Given the difference in age and education level between patients with AD and controls, these two variables were considered as covariates in the analyses. Firstly, PET images from patients with AD and controls were compared by using a

two-sample *t*-test design with the preprocessed images. Linear contrasts examined regions that showed lower metabolic activity in patients with AD than controls, and vice versa. Secondly, whole brain analyses were used to estimate the correlations between cerebral metabolism and each dependent variable: the rate of congruent responses and the AUROC2 scores for episodic and semantic tasks independently¹. Linear contrasts were set up to assess correlations between cerebral metabolism and self-awareness in each group independently, then group correlations were compared (correlations in AD > controls and controls > AD). Whole brain analyses were performed using a threshold $\alpha = 0.05$ FWE corrected for multiple comparisons at the voxel-level. Thirdly, a priori hypotheses were tested in AAL-based regions of interests (ROIs) identified by Bastin and collaborators (2021) based on previous neuroimaging studies using the FOK paradigm. For the episodic FOK, they identified the following regions: angular, cingulum anterior, cingulum posterior, frontal inferior triangularis, frontal middle, frontal superior, frontal superior medial, insula, occipital superior, parahippocampal, parietal inferior, precentral, precuneus, supplementary motor area, temporal inferior, and temporal middle. For the semantic FOK, they identified the following regions: caudate, frontal inferior orbital, frontal inferior triangularis, frontal middle, frontal superior, frontal superior medial, parietal inferior, precentral, supplementary motor area, and temporal pole middle and superior. Analyses for a priori ROIs were performed using small volume correction analyses with a threshold $\alpha = 0.05$ corrected for multiple comparisons.

¹ Since metacognitive performance was correlated between episodic and semantic FOK tasks in patients with AD, neural correlates were not analyzed in the same matrix for both FDG-PET and MRI analyses.

2.5.3. Structural MRI

All analyses were performed on SPM12 using gray matter density images from VBM. Parameters were estimated using a general linear model. Given the difference in age and education level between patients with AD and controls, these two variables were considered as covariates in all analyses. With the same schema as PET analyses, we firstly compared gray matter density from patients with AD and controls. Linear contrasts examined regions that had reduced gray matter in patients with AD than controls, and vice versa. Secondly, whole brain analyses were used to estimate the correlations between gray matter density and the rate of congruent responses and AUROC2 scores for episodic and semantic tasks independently². Linear contrasts were set up to assess correlations between gray matter density and self-awareness in each group independently, then group correlations were compared (correlations in AD > control and control > AD). Whole brain analyses were performed using a threshold $\alpha = 0.05$ FWE corrected for multiple comparisons at the voxel-level. Thirdly, a priori hypotheses were tested in the same ROIs as for PET analyses with small volume correction analyses with a threshold $\alpha = 0.05$ corrected for multiple comparisons.

3. Results

3.1. Memory and metamemory performance

Table 1 summarizes memory and metamemory scores for patients with AD and controls. Patient with AD recalled significantly fewer words than controls in the episodic, $\chi^2_{\text{Kruskal-Wallis}}(1) = 31.04, p < .001$, and semantic tasks, $\chi^2_{\text{Kruskal-Wallis}}(1) = 20.57, p < .001$. For recognition

² Since metacognitive performance was correlated between episodic and semantic FOK tasks in patients with AD, neural correlates were not analyzed in the same matrix for both FDG-PET and MRI analyses.

performance, we performed a robust ANOVA on d' values. There was no main effect of the task, $F(1,62) = 0.34, p = .57$, but a main effect of the group, $F(1,62) = 29.15, p = .001, \zeta = 0.70$. Controls have better recognition performance than patients with AD in both episodic and semantic tasks. There was no interaction between group and task, $F(1,62) = 1.75, p = .20$.

Two indices were used to estimate metamemory performance: the rate of congruent responses (i.e., proportion of hits for yes FOK responses), and the metamemory sensitivity (AUROC2). Results showed a main effect of the group on congruence, $F(1,62) = 15.78, p < .001, \eta^2g = 0.16$, with fewer congruent responses for patients with AD than controls. There was no main effect of task, $F(1,62) = 1.49, p = .23$, but an interaction effect between group and task, $F(1,62) = 6.89, p < .01, \eta^2g = 0.03$. The difference between episodic and semantic tasks was higher in patients with AD than in controls. To verify that these results are due to a difficulty of patients to monitor their judgments and not to a tendency to underestimate memory performance (i.e., general tendency for “No” responses), the total number of “Yes” FOK responses were compared between patients and controls. Results showed no difference between patients with AD and controls in either the episodic task, $\chi^2_{\text{Kruskal-Wallis}}(1) = 2.48, p = .12$, or the semantic task, $\chi^2_{\text{Kruskal-Wallis}}(1) = 2.48, p = .12$.

AUROC2 scores of patients with AD were significantly different from chance in both episodic, $t(39) = 2.19, p = .03, d = 0.35$, and semantic tasks, $t(38) = 2.49, p = .02, d = 0.40$, suggesting that patients with AD are able to monitor their metamemory judgments. Moreover, there was no main effect of group on AUROC2 scores, $F(1,61) = 1.05, p = .31$, no main effect of task, $F(1,61) = 0.78, p = .38$, and no interaction effect between group and task, $F(1,61) = 2.41, p = .13$.

For the Remember/Know procedure, patients with AD reported fewer Remember responses than controls, $t(32.08) = -6.38, p < .001, d = -1.67$. The proportion of Know responses did not differ between the two groups, $t(67.62) = 1.23, p = .11, d = 0.29$. The proportion of Remember responses in the episodic FOK task was correlated with the proportion of congruent responses ($r = 0.68, p < .001$), but not with the AUROC2 scores ($r = 0.21, p = .09$).

Table 1

Mean and standard deviations of memory (recall and recognition) and metamemory (rate of congruent responses and metamemory accuracy) performance for Alzheimer patients (AD) and healthy older controls in the episodic and semantic FOK paradigm.

	Task	Patients with AD	Controls
Cued Recall (percentage of correct responses)	Episodic	5.38% (10.8)	35.2% (24.60) ***
	Semantic	13.40% (13.60)	39.40% (22.00) ***
Recognition (d')	Episodic	0.95 (0.57)	1.66 (1.16) ***
	Semantic	1.20 (0.42)	1.77 (0.5) ***
Congruency (percentage of hit/yes responses)	Episodic	34.80% (25.80)	67.10% (23.60) ***
	Semantic	45.60% (18.10)	65.00% (17.30) ***
Percentage of "Yes" responses	Episodic	62.20% (37.30)	81.70% (17.10) ns
	Semantic	76.80% (26.10)	88.80% (11.70) ns

Metamemory accuracy (AUROC2)	Episodic	0.53 (0.10)	0.56 (0.12) ^{ns}
	Semantic	0.53 (0.08)	0.51 (0.11) ^{ns}
Recollective experience (proportion of each response on hits)	Remember	0.06 (0.12)	0.47 (0.33) ^{***}
	Know	0.34 (0.32)	0.26 (0.23) ^{ns}

Note. Testing difference between Alzheimer patients and controls: ns. non-significant; * $p < .05$; *** $p < .001$.

3.2. Neuroimaging data: Group comparison

Whole brain analyses compared patients with AD and controls to highlight group differences in metabolism and gray matter density. Images from FDG-PET showed that, compared to controls, patients with AD had hypometabolism in a large cluster centered on the right middle cingulate cortex extending to temporoparietal cortex, posterior midline regions, and bilateral frontal regions (Table 2). Group comparison of MRI images showed that AD patients had reduced gray matter density compared to controls in the right superior occipital area and in the right middle temporal region. Table 2 presents the coordinates of peak voxels showing significant differences between patients with AD and controls from whole brain analyses. Control participants showed neither hypometabolism, nor reduced gray matter density in any brain region compared to patients with AD.

Table 2

Significant differences in metabolism (PET) and gray matter density (MRI) between Alzheimer patients and controls from whole brain analyses.

Method	Region (from AAL atlas)	MNI coordinates			Z score	Cluster size
		x	y	z		
PET	Right Cingulum Middle	3	-46	34	6.51	118840
	Right Parietal Inferior	33	-46	49	6.23	584
	Left Frontal Inferior Operculum	-39	8	25	5.08	513
	Left Frontal Middle Orbital	-24	41	-14	5.04	263
	Left Occipital Inferior	-51	-61	-14	4.90	67
	Left Calcarine	-15	-100	-11	4.69	31
	Right Cingulum Middle	9	2	40	4.56	23
	Right Frontal Inferior Orbital	36	35	-17	4.43	39
	Right Frontal Middle	30	23	40	4.42	27
MRI	Right Occipital Superior	22	-90	36	5.42	404
	Right Temporal Middle	64	-32	2	4.89	1013

3.3. Brain metabolism and self-awareness

Whole-brain correlation analysis between glucose metabolism and metamemory scores (i.e., congruence and AUROC2) did not show any significant regions with the threshold $\alpha = 0.05$ corrected for multiple comparisons. Table 3 summarizes significant correlations between metamemory scores and brain metabolism with the small volume correction analyses on a priori ROIs. In patients with AD, the rate of congruent responses in the episodic FOK was more correlated with metabolism of the right precuneus, than for controls (AD > controls). In patients with AD only, the rate of congruent responses also correlated positively with metabolism of the right middle and superior frontal cortex, right inferior parietal cortex, right precentral cortex, and right middle temporal cortex.

Whole-brain correlation analysis between glucose metabolism and proportion of Remember and Know responses did not show any significant regions with the threshold $\alpha = 0.05$ corrected for multiple comparisons.

Table 3

Significant correlations between metamemory scores and changes in brain metabolism (FDG-PET) in the regions of interests (ROIs) for Alzheimer patients only (AD) and compared with regressions observed in controls.

Region	MNI coordinates			Z score	Cluster size
	x	y	z		
Episodic FOK (congruency)					
<i>Correlation in AD > controls</i>					
Right precuneus	15	-40	43	3.38	2
<i>Correlations in AD</i>					
Right frontal middle	36	29	46	3.46	77
Right frontal superior medial	12	29	43	3.12	2
Right parietal inferior	42	-40	43	3.17	1
Right precentral	63	2	22	3.64	12
Right precuneus	9	-55	16	3.27	3
Right temporal middle	63	-19	-17	3.28	11

Note. AD = patients with Alzheimer disease; FOK = feeling-of-knowing. The congruency was estimated with the proportion of hit/yes responses. Other scores and contrasts showed no significant regressions in the ROIs.

3.4.Gray matter density and self-awareness

Whole-brain correlation analyses between gray matter and metamemory scores (i.e., congruence and AUROC2) did not show any significant regions with the threshold $\alpha = 0.05$ corrected for multiple comparisons. Table 4 summarizes significant correlations between metamemory scores and gray matter density with the small volume correction analyses on a priori ROIs. In patients with AD, the rate of congruent responses in the semantic FOK was more correlated with gray matter density of the left angular gyrus, than for controls (AD > controls).

Table 4

Significant correlations between metamemory scores and changes in gray matter density (structural MRI) in the regions of interests (ROIs) for Alzheimer patients (AD) and compared with correlations observed in controls.

Region	MNI coordinates			Z score	Cluster size
	x	y	z		
Semantic FOK (congruency)					
<i>Correlation in AD > controls</i>					
Left angular	-46	-66	36	3.47	8

Note. AD = patients with Alzheimer disease. The congruency was estimated with the proportion of hit/yes responses. Other scores and contrasts showed no significant regressions in the ROIs.

Whole-brain correlation analysis between gray matter density and proportion of Remember and Know responses independently did not show any significant regions with the threshold $\alpha = 0.05$ corrected for multiple comparisons.

4. Discussion

The aim of this study was to assess the previously untested dissociation between episodic and semantic metamemory in AD using a FOK paradigm, and to explore the neural correlates associated with these two metamemory processes independently. We expected that patients with AD would have difficulties to evaluate their memory performance compared to elderly controls, and more so when the episodic component was involved. Furthermore, we hypothesized that anosognosia of memory deficits was related to changes in glucose metabolism (FDG-PET) and gray matter integrity (structural MRI) in patients with AD.

Results showed that patients with AD had fewer congruent responses (i.e., “Yes” FOK followed by a hit) compared to controls, testifying of their difficulties to predict future recognition. This result cannot be explained by a tendency of patients with AD to underestimate memory performance (as shown by Genon et al., 2016), since the total number of “Yes” and “No” responses in the FOK paradigm did not differ between patients and controls. As expected, the difference between episodic and semantic tasks was larger in patients with AD than in controls. Patients with AD had less congruent responses in the episodic FOK task than in the semantic FOK task.

The partial retrieval hypothesis argues that FOK judgements are based on the recollection of partial information about the target (Koriat, 1993). Thus, the episodic FOK deficit in AD could result from a recollection deficit (Souchay & Moulin, 2009). The results from the

Remember/Know procedure are in line with this hypothesis. Patients with AD reported fewer recollective experiences than controls. The reduction of Remember responses in AD may be due to patients' difficulty in re-experiencing an event (i.e., auto-noetic consciousness) (Rauchs et al., 2007), and recollecting spatiotemporal information relating to it (Barba, 1997; Rauchs et al., 2007). Thus, metamemory judgments of patients with AD may be based on (less reduced) cue familiarity rather than recollection of partial information of the target, leading to inappropriate metamemory judgments (Souchay & Moulin, 2009). In line with this hypothesis, the proportion of congruent responses was correlated with the proportion of Remember responses. Patients with fewer recollective experiences also had less congruent judgments.

The decrease in memory awareness in AD was not shown using measures of metamemory accuracy (i.e., AUROC2) in both episodic and semantic tasks. Congruence of judgments and metamemory accuracy rely on distinct processes and neural correlates in AD (Bastin et al., 2021; Bertrand et al., 2018). Thus, this dissociation was also shown in our results. Patients with AD had difficulties in making judgments (i.e., absolute accuracy), but were able to adapt their judgments according to their memory performance (i.e., relative accuracy).

In line with previous studies (Bertrand et al., 2018; Elman et al., 2012; Hallam et al., 2020), the results suggest that the right frontal lobe is involved in the congruence of episodic metamemory judgments of patients with AD. The role of the frontal lobe in episodic metamemory has been observed from the earliest stages of the disease. The congruence of FOK judgments in an episodic task is correlated with hypometabolism of the right superior frontal and the middle frontal regions in MCI patients who subsequently developed AD (Bastin et al., 2021). In healthy adults, metamemory tasks activate the inferior frontal gyrus (Kikyo et al., 2002). This region therefore appears to be linked to both anosognosia and metamemory processing. Frontal lobes are known to be involved in the monitoring process (Ernst et al.,

2015; Souchay, 2007; Souchay & Moulin, 2009). Thus, a dysfunction and the loss of the gray matter integrity of lateral frontal regions could lead to inappropriate metamemory judgments.

Associated with this frontal impairment, episodic FOK congruence of patients with AD was linked with glucose metabolism in the right middle temporal cortex. It has already been shown that the severity of anosognosia is related with the gray matter integrity of the middle temporal cortex (Hallam et al., 2020). The changes observed in this region leads to difficulties of patients with AD to update the information stored in the personal database present in the CAM (Salmon et al., 2024). Moreover, episodic FOK congruence seems to be linked to the hypometabolism of structures that harbor AD related neuropathology, as these regions also show reduced metabolism in the group comparison. Thus, episodic FOK congruence may be particularly sensitive to AD because it relies on brain regions that are affected by the disease.

Taken together, the results suggest the involvement of the default mode network (DMN) in memory awareness. The brain atrophy, amyloid plaques, and reduced glucose metabolism observed in AD also affect the DMN (Hafkemeijer et al., 2012). The present results suggested that episodic FOK congruence was correlated with the brain metabolism in the right precuneus, right inferior parietal cortex and right superior frontal cortex, and with the gray matter integrity in the semantic FOK with left angular gyrus. These regions are part of the DMN. It was already known that self-awareness implies the DMN (Antoine et al., 2019; Chua et al., 2009; Hallam et al., 2020; Mevel et al., 2011). Higher anosognosia is related with hypometabolism and reduced cerebral activations in the posterior cingulate cortex and the precuneus (Mondragon et al., 2019; Salmon et al., 2024). In their review, Salmon et al. (2024) shows that these two regions play an important role in the integration of information in memory. Changes in these regions observed in AD could lead to reduce access to information about previous performance, which has been poorly encoded. Similarly, the left inferior lobule is involved in retrieving

complex information in memory (Salmon et al., 2024). Thus, anosognosia may result from a disconnection between episodic memory (supported by the medial temporal subsystem of the DMN), the personal database (supported by the middle temporal cortex), and the evaluative system (supported by the core system of the DMN) (Antoine et al., 2019).

To conclude, while previous studies explored episodic and semantic metamemory independently in AD, this study clearly showed the dissociation of these two processes in the same patients. Patients had more difficulties to predict their recognition in the episodic task than in the semantic task. Nevertheless, this result is only observed when using absolute accuracy (i.e., congruence of responses), and not relative accuracy (estimated with AUROC2). The reduced memory awareness in AD is related to hypometabolism or loss of gray matter density in the frontal regions, the precuneus, parietal regions, and middle temporal cortex. In line with previous studies (Antoine et al., 2019; Salmon et al., 2024), these results suggest that anosognosia results from damage to regions underlying self-related processes and episodic memory. Moreover, the results support the involvement of the DMN in self-awareness. Given that the brain modification related to anosognosia are perceptible in the preclinical phase of the disease (Bastin et al., 2021; Vannini et al., 2019), exploring the neural correlates of memory awareness can help identify biomarkers that could be used for early diagnosis of AD.

Disclosure Statement

We declare that there are no conflicts of interest exist related to this study.

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