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ABSTRACT

Patients with Alzheimer's disease (AD) 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 AD 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 AD were compared to data from 30 healthy controls. Results showed that patients with AD had more difficulties to predict their recognition in the episodic task than in the semantic task, while this difference was smaller in controls. However, this dissociation was only shown with a measure of absolute accuracy, but not with a measure of relative accuracy. Lack of awareness in the episodic task was associated with hypometabolism in right frontoparietal areas in patients with AD, while semantic metamemory was associated with gray matter integrity in the left angular gyrus. The consequence of metacognitive bias and memory status on metamemory judgments are discussed.

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 and 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 to define the role of memory in anosognosia (Agnew and Morris, 1998; Morris and 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 and on general knowledge about memory functioning. In the event of a mismatch between actual and expected performance, the personal database can be updated. For instance, let's imagine two older adults 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

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.

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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 and Zak, 1996).

One of the hallmarks of anosognosia in AD is the inability to assess memory performance. This 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. Two types of accuracy can be evaluated: absolute and relative accuracy. Absolute accuracy refers to a participant's tendency to favor one metamemory judgment over another (e.g., saying "Yes, I will recognize" most of the time when making a FOK judgment); while relative accuracy is the ability to adapt judgments according to memory performance. Compared to absolute accuracy, relative accuracy can be free from bias. For instance, the AUROC2 (detailed in the method section) does not depend on participants' tendency to favor a judgment, but measures their ability to distinguish between stimuli that will be remembered and those that will be forgotten (see Fleming and Lau, 2014). Absolute and relative accuracy relies on distinct processes and neural correlates (Bastin et al., 2021; Bertrand et al., 2018). Previous studies using absolute accuracy as a measure of metamemory status focused on the episodic metamemory and shown that patients with AD are overconfident about their performance (Cosentino et al., 2016; Ernst et al., 2015; Moulin et al., 2000). Using a measure of relative accuracy, patients with AD are less accurate than controls in episodic FOK tasks, but they are as accurate as healthy older 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 patients' 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 spatiotemporal cues, as well as on autonoetic 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 temporospatial 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 and 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, poor metamemory performance appears 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; Mondragón et al., 2019; Salmon et al., 2024). Furthermore, anosognosia appears to be associated with frontal lobe damage (Ernst et al., 2015; Kaszniak and Zak, 1996; Ries et al., 2012). It has been proposed that executive decline linked to the frontal lobe damage observed in AD participates to the lack of awareness (Clare et al., 2011; Ernst et al., 2015; Morris and Mograbi, 2013).

Moreover, it has been noted that most of the regions involved in cognitive awareness (i.e., both metamemory and anosognosia) are part of the default mode network (DMN) (e.g., Antoine et al., 2019; Salmon et al., 2024). The DMN is composed of several brain areas, including the posterior cingulate cortex, precuneus, and the medial prefrontal cortex, that are activated during resting state, but deactivated during goal-oriented tasks (Raichle et al., 2001). Perturbations in the DMN activations and deactivations are observed in AD (Mevel et al., 2011). It is proposed that anosognosia and metacognitive deficit in AD results from disconnections within the DMN (Antoine et al., 2019; Hallam et al., 2020; Perrotin et al., 2008).

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 explored the absolute and relative accuracy of metamemory judgments with 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 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 associative regions (Bertrand et al., 2018; Genon et al., 2016; Hallam et al., 2020).

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 older controls (20 females) took part in the experiment. Patients were recruited from the memory clinic at Liège University Hospital by their neurologist, whom they were consulting for their cognitive disorders. 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 (see "Neuropsychological Assessment" section), and the presence of biomarkers in FDG-PET (e.g., hypometabolism in parieto-temporal and posterior cingulate cortex; Herholz et al., 2002).

Control participants were recruited from the local community by word of mouth. They had no psychiatric or neurological antecedents, no anxiolytic or antidepressant medication, no excessive consumption of alcohol, and had normal or corrected hearing and vision. 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 than controls (see Table 1), $t(54.95) = 2.71$, $p < .01$. All were native French speakers and their average level of education was 10.9 years ($sd = 3.25$). Patients with AD were less educated than controls (see Table 1), $t(56.01) = -3.25$, $p < .01$. Thus, analyses of this study took age and education into account as covariates.

2.2. 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, all participants completed 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 stimuli came from a previous semantic FOK task (Izaute et al., 1996) and consisted of low-frequency French words (i.e., between 1 and 40 occurrences per million).

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 prediction. 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 prediction 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.

Table 1
Demographic data and neuropsychological scores for Alzheimer patients and controls.

	Alzheimer patients ($n = 50$)	Controls ($n = 29$)
Age (years)	77.20 (6.85)	72.90 (6.95) **
Women/Men	32/18	$20/9^{ns}$
Education (years at school)	10.10 (3.06)	12.30 (3.12) **
Mini Mental State Examination (MMSE, max = 30)	22.60 (2.90)	NA
Mattis Dementia Rating Scale (MDRS)	118 (11.30)	138 (5.96)
Memory functioning Scale(from the MARS)	0.38 (0.46)	0.01 (0.17) ***

Note. Testing difference between Alzheimer patients and controls: ns: non-significant; ** $p < .01$; *** $p < .001$.

2.3. Neuropsychological assessment

All participants completed a neuropsychological assessment to assess the cognitive status at inclusion of the two groups (patients with AD or controls) in the week before or after the neuroimaging. To avoid interference with the metamemory tasks, the neuropsychological assessment was performed after the two FOK paradigms. Each test aimed to assess a CAM component: The working-memory component was assessed with the reading span test (Desmette et al., 1995), the semantic-memory component with the Mill Hill vocabulary scales (Raven et al., 2008), the autobiographical part with the TEMPau (Episodic Test of Autobiographical Past Memory; Piolino et al., 2000), and the executive functioning component was assessed using the Hayling task (Burgess and Shallice, 1994) and the cognitive estimation task (Levinoff et al., 2006). The scores of these tests are not detailed in this article, as we preferred to focus on the assessment of general cognitive functioning.

General cognitive functioning of patients with AD was tested with the Mini Mental State Examination (MMSE; Folstein, 1975). As expected, the MMSE scores of patients with AD were below the pathological threshold, suggesting the general cognitive impairment of patients with AD. In addition, all participants were tested on the Mattis Dementia Rating Scale (MDRS; Mattis, 1976). Control participants' MDRS scores were confronted with the norms provided by Pedraza et al. (2010) and the total score was normal for each participant. Moreover, controls had better performance than patients with AD on the MDRS, $z = -6.51$, $p < .001$, $r = 0.75$, as well as on other tests. 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. Table 1 compares demographic and neuropsychological information for controls and patients with AD.

Moreover, the degree of anosognosia was tested using a discrepancy score calculating the gap between participants' perceived difficulties on a memory functioning scale and those of their relative (from the MARS-MFS; Clare et al., 2002). Patients with AD had higher discrepancy scores than controls, $z = 3.79$, $p < .001$, $r = 0.47$, suggesting anosognosia for

memory deficits at the group level.

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-[^{18}F]fluoro-2-deoxy-D-glucose (FDG, 152–290 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 back projection, 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 on 43 patients with AD and 25 controls. A high-resolution T1-weighted image (3D MDEFT) was acquired on a 3 T Siemens Allegra scanner using the following parameters: TR/TE/TI = 7.92/2.4/910 ms, FA = 15∘, FOV = 256 × 240 × 176 mm^2, 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-Duperray 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 episodic and semantic tasks 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 0.95 (Macmillan and 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 a measure of absolute and relative accuracy. Absolute accuracy was assessed using the rate of congruent responses, 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 relative accuracy: the AUROC2 (see Fleming and 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"). This ensures that the measurement is bias free (see Fleming and Lau, 2014). 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 and 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 independently.[1] 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

[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.

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 α = 0.05 corrected for multiple comparisons.

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 independently.[2] 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 α = 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 α = 0.05 corrected for multiple comparisons.

Table 2
Mean and standard deviations of memory (recall and recognition) and metamemory (rate of congruent responses and relative 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}
Relative 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 < .001.

[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.

3. Results

3.1. Memory and metamemory performance

Table 2 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 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, $F(1,62) = 29.15$, $p = .001$, $\xi = 0.70$. 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, $F(1,62) = 15.78$, $p < .001$, $\eta^2 g = 0.16$, 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, $F(1,62) = 6.89$, $p < .01$, $\eta^2 g = 0.03$. The difference between episodic and semantic tasks was higher in patients with AD than in controls (see Fig. 1). 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, $F(1,61) = 2.41$, $p = .13$. Fig. 2 shows the distribution of AUROC2 scores in episodic and semantic tasks in both groups.

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 ($r = 0.21$, $p = .09$). Fig. 3 illustrates these correlations.

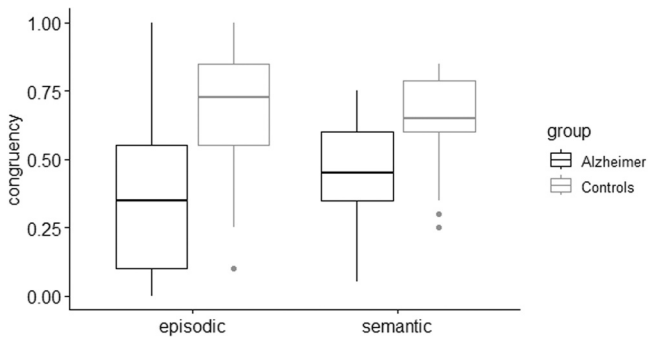

Fig. 1. Rate of congruent responses (i.e., proportion of hits for yes FOK responses) in episodic and semantic tasks for patients with Alzheimer's disease and healthy older adults (controls).

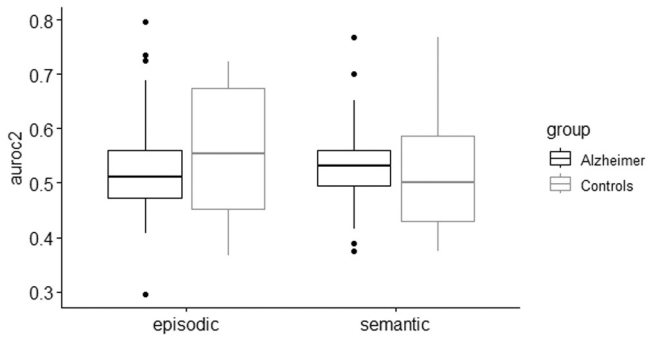

Fig. 2. Metamemory sensitivity (measured with AUROC2) in episodic and semantic tasks for patients with Alzheimer's disease and healthy older adults (controls).

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 3). 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 3 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.

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 4 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 analyses 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.

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 5 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

Table 3
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

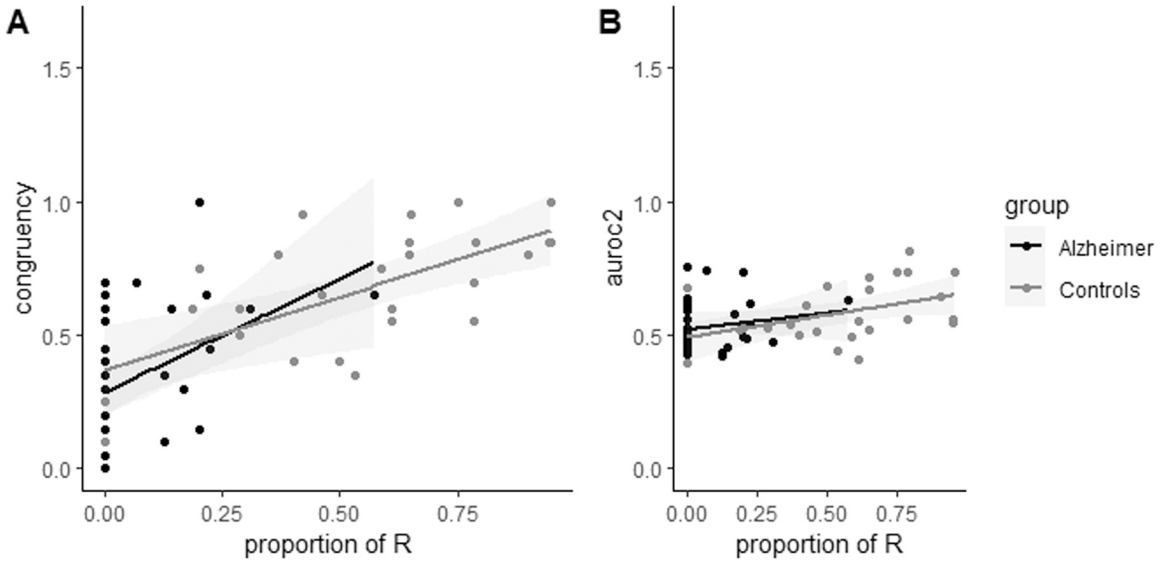

Fig. 3. Correlation between the proportion of Remember responses (R) in the recognition phase of the episodic FOK task and both metamemory measures: (A) the rate of congruent responses (i.e., proportion of hits for yes FOK responses), and (B) metamemory sensitivity (measured with AUROC2).

Table 4
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)					
Correlation in AD > controls					
Right precuneus	15	−40	43	3.38	2
Correlations in AD					
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.

Table 5
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)					
Correlation in AD > controls					
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.

congruent responses in the semantic FOK was more correlated with gray matter density of the left angular gyrus, than for controls (AD > controls).

Whole-brain correlation analyses 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 older controls, and more so when the episodic component was involved. Furthermore, we hypothesized that metamemory deficits were 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. 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.

However, the decrease in memory awareness in AD was not shown using measures of relative accuracy (i.e., AUROC2) in both episodic and semantic tasks. In line with previous studies in older adults and people with mild cognitive impairment (MCI) (Bastin et al., 2021; Bertrand et al., 2018), our results showed that absolute and relative accuracy rely on different processes. Compared to the congruence measure, AUROC2 is independent of metacognitive bias (e.g., participants' tendency to always say "No" for FOK judgment). Although the number of "Yes" responses in FOK judgments did not differ significantly between controls and patients, there was considerable variability between participants, particularly for patients with AD (standard deviation of 37.30 in the episodic task, and of 26.10 in the semantic task). This variability may be explained by the fact that some patients with AD gave only one type of response (i.e., only "Yes" or only "No" responses) in the FOK judgments. Thus, the average "Yes" response is not significantly different between controls and patients, due to the variability inherent in measuring metacognitive bias. Both types of bias (i.e., underestimation and overestimation) are present in patients with AD. Previous studies have also shown that most patients with AD overestimate their memory performance, but a smaller proportion underestimate it (e.g., Clare et al., 2010). Thus, it seems to us that metacognitive bias could influence analyses of the congruence measure. The decline in the accuracy related to episodic metamemory judgment observed in AD could be due to a metamemory bias, rather than an inability to adapt metamemory judgments related to memory performance.

Nevertheless, it is important to note that both the congruence measure and AUROC2 are dependent on memory performance (Fleming and Lau, 2014). The results can be influenced by differences in rates of correct recognition between controls and patients (i.e., controls participants recognized more words than patients with AD). Other metamemory measures are more independent of memory performance, such as the Mratio (Maniscalco and Lau, 2012; 2014). However, we were reluctant to use these types of measures because they require a larger number of trials to be reliable (Guggenmos, 2021), which is difficult to implement in a clinical population with cognitive difficulties (mainly attention and memory).

To make the tasks achievable by patients with AD, we decided to use a Yes/No design for the FOK judgments instead of graded probability judgments. A future study could compare different memory domains across different types of judgments in the same patients to explore the various dissociations within metamemory in AD (see Mazancieux et al., 2020 for an example of paradigm in younger adults). It has already been observed that older adults with MCI appear to be particularly accurate in assessing the current state of their performance during an ongoing task, which could be essential in regulating their behavior to implement compensatory strategies and achieve greater cognitive independence (Piras et al., 2016). Similarly, patients with AD are able to detect their episodic memory errors (Gallo et al., 2012; Geurten et al., 2021; Moulin et al., 2003). However, patients with AD make inaccurate confidence judgments compared to healthy controls in episodic tasks (Dodson et al., 2011). In the current study, we did not systematically record participants' reactions during the task, so that we cannot evaluate error detection.

The partial retrieval hypothesis argues that FOK judgements are based on the recollection of partial information about the target (Koriat, 1993). Thus, it is proposed that the episodic FOK deficit observed in AD could result from a recollection deficit (Souchay and 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., autonoetic 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 and 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. Consistently with the cognitive awareness model (CAM; Agnew and Morris, 1998; Morris and Mograbi, 2013), this result suggests that metamemory judgments (partly) rely on memory processes (Antoine et al., 2019).

In line with previous studies (Bertrand et al., 2018; Elman et al., 2012; Hallam et al., 2020) and our hypotheses, 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 and 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). Thus, the neural correlates associated with episodic metamemory deficit appear to be related to those of anosognosia. The changes observed in the right middle temporal cortex leads to difficulties for 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. Within the DMN, and in line with our results, the posterior cingulate cortex and precuneus are associated with episodic memory and self-referential processes, while the lateral parietal cortex is associated with semantic processing (Mevel et al., 2011). This could explain why episodic FOK and semantic FOK are associated with different regions in our results.

To focus on the posterior cingulate cortex and the precuneus, hypometabolism and reduced cerebral activations in these regions are related with higher anosognosia in AD (Mondragón 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 reduced 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).

The neural correlates of consciousness are difficult to identify, as many regions are involved and networks are extensive (see Yaron et al., 2022), giving rise to a risk of spurious findings and interpretations bias. In our study, it is important to note that not all participants did the FDG-PET (we had no data for 18 patients with AD and 7 controls) and the structural MRI (no data for 7 patients with AD and 5 controls). Consequently, there was a drop of statistical power between behavioral and neuroimaging data. Given the difficulty of recruiting patients with AD, who moreover can perform neuroimaging study, and the complexity of cognitive awareness networks, literature reviews and meta-analysis are crucial in this field to combine data and identify clinical features explaining awareness state (e.g., see Hallam et al., 2020; Mondragón et al., 2019; Salmon et al., 2024).

To conclude, while previous studies explored episodic and semantic metamemory independently in AD, this study showed the dissociation of these two processes in the same patients only with a measure of absolute accuracy (i.e., congruency), but not with a measure of relative accuracy (i.e., AUROC2). This difference in results between absolute and relative accuracy suggests that the metamemory deficit in AD is primarily due to a metacognitive bias, rather than an inability to adapt judgment to memory performance. 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 metamemory deficit results from damage to regions underlying self-related processes and episodic memory. Similarly, the results of the Remember/Know procedure showed that the decline in absolute accuracy could result from the recollection deficit observed in AD. Thus, our results highlighted the role of episodic status in the metamemory judgments of patients with AD. Given that the brain modification related to metamemory deficit 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.

Verification

We certify that this work has not been previously published, nor it is not under consideration for publication elsewhere. This publication is approved by all authors and by the responsible authorities where the work was carried out. If the work is accepted, we undertake not to publish it elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder

CRediT authorship contribution statement

Meunier-Duperray Lucile: Writing – original draft, Visualization, Formal analysis. **Bastin Christine:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Salmon Eric:** Writing – review & editing, Methodology, Conceptualization. **Angel Lucie:** Writing – review & editing, Funding acquisition. **Souchay Céline:** Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

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

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Data Availability

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

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