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Neural Correlates of Anosognosia for Cognitive Impairment in Alzheimer's Disease

Eric Salmon,[1]* Daniela Perani,[2] Karl Herholz,[3,4] Patricia Marique,[1] Elke Kalbe,[3,4] Vjera Holthoff,[5] Xavier Delbeuck,[1] Bettina Beuthien-Baumann,[6] Oriana Pelati,[3,4] Solange Lespagnard,[1] Fabienne Collette,[1] and Gaëtan Garraux[1]

[1]*Cyclotron Research Centre, University of Liege, Liege, Belgium*
[2]*Vita Salute San Raffaele University, Institute of Bioimaging and Molecular Physiology, CNR, IRCC Hospital San Raffaele, Milan, Italy*
[3]*Department of Neurology, University of Cologne, Cologne, Germany*
[4]*Max-Planck Institute for Neurological Research, Cologne, Germany*
[5]*Department of Psychiatry and Psychotherapy, Dresden University of Technology, Dresden, Germany*
[6]*Department of Nuclear Medicine, Dresden University of Technology and PET-Center, Research Center Rossendorf, Dresden, Germany*

Abstract: We explored the neural substrate of anosognosia for cognitive impairment in Alzheimer's disease (AD). Two hundred nine patients with mild to moderate dementia and their caregivers assessed patients' cognitive impairment by answering a structured questionnaire. Subjects rated 13 cognitive domains as not impaired or associated with mild, moderate, severe, or very severe difficulties, and a sum score was calculated. Two measures of anosognosia were derived. A patient's self assessment, unconfounded by objective measurements of cognitive deficits such as dementia severity and episodic memory impairment, provided an estimate of impaired self-evaluative judgment about cognition in AD. Impaired self-evaluation was related to a decrease in brain metabolism measured with 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in orbital prefrontal cortex and in medial temporal structures. In a cognitive model of anosognosia, medial temporal dysfunction might impair a comparison mechanism between current information on cognition and personal knowledge. Hypoactivity in orbitofrontal cortex may not allow AD patients to update the qualitative judgment associated with their impaired cognitive abilities. Caregivers perceived greater cognitive impairments than patients did. The discrepancy score between caregiver's and patient's evaluations, an other measure of anosognosia, was negatively related to metabolic activity located in the temporoparietal junction, consistent with an impairment of self-referential processes and perspective taking in AD. *Hum Brain Mapp 27: 588–597, 2006.*

Key words: dementia; neuroimaging; cognition; awareness; evaluation; self; perspective taking; beliefs; confabulation

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*Correspondence to: Eric Salmon, Cyclotron Research Centre, University of Liege, B30 Sart Tilman, 4000 Liege, Belgium.
E-mail: eric.salmon@ulg.ac.be

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INTRODUCTION

Lack of awareness, anosognosia, or loss of insight are used interchangeably to describe the impaired judgment of patients with Alzheimer's disease (AD) concerning their own cognition, mood, behavior, or daily activities. Questionnaires are used frequently in the literature for assessing loss of insight into dementia symptoms [Migliorelli et al., 1995a]. A discrepancy score is calculated between answers obtained from the patient and from a caregiver, and this score is used as a measure of anosognosia. Self-rating of cognitive deficits is also proposed as an index of cognitive unawareness, because probable AD patients who report only benign cognitive impairment do present anosognosia [Cummings et al., 1995]. Not surprisingly, the degree of unawareness of cognitive deficits varies according to different assessment methods [Derouesne et al., 1999].

Different variables may influence the evaluation of anosognosia. Anosognosia has sometimes been said to increase over time in AD. However, in other reports there was no relationship with demographic variables such as age, education, age at onset, or duration of illness [Sevush and Leve, 1993; Starkstein et al., 1997; Vasterling et al., 1997]. Lack of awareness of AD patients was also correlated to dementia severity in most, but not all studies [Gil et al., 2001; McDaniel et al., 1995; Sevush and Leve, 1993; Zanetti et al., 1999]. The relationship between anosognosia and depression is a matter of discussion in the literature [Cummings et al., 1995; Migliorelli et al., 1995b], whereas apathy in AD was associated with poor awareness of both cognitive and behavioral changes [Starkstein et al., 2001]. Specific relationships were sought between lack of awareness of cognitive deficits and performance on neuropsychological tests. Anosognosia in AD subjects was associated in some but not all studies with memory impairment [Dalla Barba et al., 1995; Reed et al., 1993], and a relationship was frequently suggested between lack of awareness of cognitive dysfunction and impairment in specific "frontal" tests [Dalla Barba et al., 1995; Lopez et al., 1994; Michon et al., 1994; Ott et al., 1996]. All those parameters may be viewed as confounding factors that contribute to but do not explain anosognosia in dementia.

Accordingly, the neural substrate of anosognosia is a matter of debate in the literature. Different brain regions have been implicated in anosognosia for different neurological disorders, such as neglect, hemiparesis, aphasia, cortical blindness, or profound amnesia. Lack of awareness was reported in patients with diverse frontal lobe pathologies [Alexander and Stuss, 2000; McGlynn and Schacter, 1989]. In the functional imaging literature, medial prefrontal and posterior cingulate cortices were shown to be part of a neural network subserving self-reflective thoughts in normal subjects [Johnson et al., 2002; Kelley et al., 2002]. In AD, few studies have used functional imaging to characterize the brain correlates of loss of insight. In AD patients with anosognosia for cognitive deficits, a significant decrease of perfusion was reported in the lateral frontal regions, predominant on the right side [Derouesne et al., 1999; Reed et al., 1993; Starkstein et al., 1995; Vogel et al., 2005]. Preferential right-sided frontal and parietal blood flow decreases were also reported in AD patients with anosognosia [Leys et al., 1989]. The findings might be dependent on how anosognosia was assessed for the analysis. Moreover, relatively small samples of patients were included and memory, executive performances, dementia, and depression severity were not controlled in each study.

The objective of this report was to study the brain correlates of two measures of anosognosia for cognitive impairment in AD, taking multiple confounding variables into account. We analyzed data collected in a large number of probable AD patients from different positron emission tomography (PET) centers participating in a European research program (Network for Efficiency and Standardization of Dementia Diagnosis; NEST-DD). A research questionnaire on cognitive abilities was used [Kalbe et al., 2005] and three dependent variables were taken into account: caregiver evaluation of the patient's cognitive dysfunction, self-evaluation of AD patients, and the discrepancy score between caregivers and patients. Patient self-evaluation and the discrepancy score reflected two types of anosognosia for cognitive impairment in AD [Cummings et al., 1995; Migliorelli et al., 1995a]. Multiple regression and stepwise regression analyses were used to highlight clinical variables that were related to and predictive of our different cognitive evaluation scores. Those clinical data were then used as confounding variables in a clinico-metabolic correlation analysis using functional imaging obtained in all AD patients. This aimed at revealing the neural substrate characteristic of the "unawareness" component of self-evaluation of cognitive dysfunction and of the discrepancy score between caregivers and patients. We hypothesized that impaired self-evaluation of cognition in AD patients (inability to prevent false beliefs or confabulation) would be related to decreased orbitofrontal activity [Benson et al., 1996; Schnider et al., 2000b; Tucker et al., 1995]. The discrepancy score contrasted the patient's perspective on his cognition with that of a caregiver; we hypothesized that a relationship would be found with activity in the neural network recruited for perspective taking [Ruby and Decety, 2004; Vogeley et al., 2001].

PATIENTS AND METHODS

Patients (n = 209) were diagnosed as demented according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV) and criteria for probable AD followed the NINCDS-ADRDA recommendations [APA, 1994; McKhann et al., 1984]. The diagnosis was based on clinical history, general medical examination, neuropsychological tests, and laboratory results. Vascular risk factors were evaluated by the Hachinski score [Hachinski et al., 1975]. Neuroanatomical imaging data were examined to rule out major vascular lesions. Leukoaraiosis was not considered as an exclusion criterion in our study. Differential diagnosis was also controlled using clinical criteria for frontotemporal dementia [Neary et al., 1998], Lewy body disease [McKeith et al.,

1996], Parkinson's disease [Gelb et al., 1999], mild cognitive impairment [Petersen et al., 1999], and depression [APA, 1994]. Each patient (or a close relative) gave informed consent to participate in the study and the protocol was accepted by the local Ethics Committee of each participating center.

Research Questionnaire for Evaluation of Anosognosia

An experimental questionnaire was designed for NEST-DD to obtain patient and caregiver assessments of multiple cognitive domains for each patient [Kalbe et al., 2005]. Multiple domains were chosen to cover the spectrum of possible symptoms in the different types of dementia studied in NEST-DD. The 13 selected cognitive domains were memory, attention, temporal and spatial orientation, verbal fluency, word finding, reading, writing, executive function, abstract thinking, praxis, number processing, and calculation. For each domain, rating was relatively simple and corresponded to five levels: no complaints (1); mild difficulties (2, infrequent with few repercussions on daily activities); moderate difficulties (3, more than mild disturbances, but not severe); severe problems (4, definitely disturbing and frequent); or very severe impairment (5, profoundly disturbing). The sum score ranged from 13 to 65. The sum score was used to increase variability in our regression and correlation analyses. The principle of the rating was first explained to the subject, who was explicitly required to refer to the present time (the last months) when making evaluation. Subjects had to be well awake and cooperative, and they had to understand the meaning of the rating to start the questionnaire. Stereotyped questions then were proposed to describe the cognitive domain being assessed (e.g., to assess attention or distraction: "do you [does he/she] have problems in following a conversation or in concentrating on reading or watching TV? Do you [does he/she] easily get distracted?"). Subjects were subsequently asked to rate recent difficulties in the given domain.

Three dependent variables were analyzed: the total score corresponding to caregiver evaluation of the patient's cognitive impairment, the total score reflecting cognitive self-evaluation of the AD patient (self-evaluation), and a differential score calculated by subtraction of patient from caregiver total score (the discrepancy score).

Clinical Variables

We capitalized on the literature in AD to select, in the general protocol of our European research project, 16 potentially predictive variables for anosognosia (Table I). Demographic variables were age, education (in years), and disease duration (in months). Dementia scales comprised the Mini-Mental State Exam [MMSE; Folstein et al., 1975], the Clinical Dementia Rating scale [CDR; Hughes et al., 1982], and the Instrumental Activity of Daily Living scale [IADL; Lawton and Brody, 1969]. Our population comprised 36 patients with CDR score 0.5, 135 with CDR score 1, and 38 with CDR score 2. Mood and behavioral assessment comprised the 21-item version of the Hamilton depression scale [Hamilton, 1967] and anxiety, apathy, and dysphoria subscores of the Neuropsychiatric Inventory [NPI; Cummings et al., 1994]. Selected neuropsychological scores were delayed free recall from the California Verbal Learning Test [CVLT; Delis et al., 1987], delayed recall for Rey's complex figure [Spreen and Strauss, 1998], forward digit span [Wechsler, 1997], mental control subtest from the Wechsler Memory Scale [Wechsler, 1997], semantic fluency (animals), and phonemic fluency (letters). Scores from fluency tasks were normalized in each center using Z-scores to take age into account. Mean Hachinski score was 1.33 ± 1.30. Sixty-nine patients had a relative with dementia. The most frequently used medications were cholinesterase inhibitors (n = 89), antihypertensive treatments (n = 65), platelet antiaggregants (n = 55), antidepressants (mainly serotonin reuptake inhibitors; n= 39), benzodiazepines (n = 34), cardiac treatments (n = 27), and hypolipemiants (n = 26).

TABLE I. Demographic and clinical data of the Alzheimer's disease population

Parameter	Mean ± SD	Range
n (M/F)	209 (71/138)	
Age (yr)	70 ± 8	49–86
Education (yr)	9 ± 4	4–20
Disease duration (months)	35 ± 22	6–120
MMSE	20.95 ± 4.45	10–28
CDR	1.13 ± 0.58	0.5/1/2
IADL (% of maximal score)	46 ± 17	24–87
Hamilton depression score	4.27 ± 4.73	0–22
NPI anxiety	1.58 ± 2.47	0–12
NPI apathy	1.77 ± 2.97	0–12
NPI dysphoria	1.46 ± 2.56	0–12
CVLT (delayed free recall)	1.57 ± 2.26	0–10
Rey's figure (delayed recall)	3.12 ± 4.21	0–22
Forward digit span	5.18 ± 1.68	1–10
Mental control	3.76 ± 1.94	0–6
Semantic fluency (Z-scores)	−1.70 ± 1.07	−3.79–0.62
Phonemic fluency (Z-scores)	−0.88 ± 0.97	−2.58–2.29

MMSE, Mini-Mental State exam; CDR, Clinical Dementia Rating; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatric Inventory; CVLT, California Verbal Learning Test.

Multiple regression analyses were carried out in *Statistica* (StatSoft, Maisons-Alfort, France; http://www.statsoft.com) to determine which clinical data were related to our dependent variables (the three measures obtained from the questionnaire of cognitive evaluation). We reported all correlations with a P value less than 0.05, because the variables were discussed previously in the literature on anosognosia. Positive or negative correlations allowed interpretation of the meaning of the relationships. Stepwise regression analyses then provided a model where different clinical data contributed to explain caregiver assessment of cognitive function in AD and the two measures reflecting anosognosia for cognitive impairment.

PET Acquisitions

We capitalized on a previous study of AD to gather PET images from five different centers [Herholz et al., 2002]. Data

were acquired with PET scanners that differed with respect to field of view and spatial resolution [Herholz et al., 2002]. Studies were carried out during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of 110–370 MBq 18F-2-fluoro-2-deoxy-D-glucose (FDG-PET). Images of tracer distribution in the brain were used for analysis; the required minimum scan starting time was 30 min after tracer injection. Scan duration was generally 20 min. Images were reconstructed using filtered backprojection including correction for measured attenuation and scatter using standard software as supplied by the various scanner manufacturers.

Image Processing and Analysis

Basic image processing and voxel-based data analyses were carried out using statistical parametric mapping (*SPM99*) routines (Wellcome Department of Cognitive Neurology, London, UK) implemented in *MATLAB* (The Mathworks, Sherborn, MA). In the coordinating center (Cologne), all data were checked and spatially normalized by affine 12-parameter transformation using the SPM99 standard Montreal Neurological Institute (MNI) brain template. Normalized images were represented on a $79 \times 95 \times 68$ matrix with $2 \times 2 \times 2$-mm voxel size. Images were transferred to the Liege center and smoothed using a 12-mm full-width half-maximum (FWHM) isotropic kernel. Correlations between brain metabolism and our three dependent variables were estimated according to the general linear model using linear contrasts; global activity adjustment was carried out using proportional scaling. The resulting set of voxel values for each analysis constituted a map of the T statistic (SPM[T]), thresholded at $P < 0.05$, voxel level, corrected for multiple comparisons. We also reported correlations obtained at $P < 0.001$, uncorrected for multiple comparisons because a complex design matrix was used for the analyses. Cluster size was greater than 30 voxels. Variables of interest were caregiver and self-evaluation of cognitive dysfunction and the discrepancy score between caregivers and patients, whereas confounding covariates were age and MMSE score (classically used in PET studies of AD patients) and the other clinical variables significant in the respective stepwise regression analyses.

RESULTS

Correlations Between Cognitive Evaluations

As expected, there was a relationship between the discrepancy score for cognitive impairment on the one hand, and cognitive evaluation by the patient (Pearson test, $r = -0.396$, $P < 0.001$) and the caregiver ($r = 0.675$, $P < 0.001$) on the other hand, because the former is mathematically derived from the two others. There was a positive correlation between patient and caregiver evaluations ($r = 0.410$, $P < 0.001$). The range of values given by caregivers was greater than that reported by patients, however, and on average, caregivers perceived greater impairment than patients did. The mean caregiver evaluation score was 26.5 $\pm$ 8.3 (corresponding to mild cognitive impairment in most AD patients with CDR score 1), the mean patient evaluation score was 21.2 $\pm$ 6.3 (significantly lower than the caregiver's score using a *t*-test, $P < 0.0001$), and the mean differential score between caregiver and patient evaluation was 5.3 $\pm$ 7.9. Consequently, patients' cognitive evaluations seemed to correspond on average to an underestimation of their cognitive impairment; this assessment partly reflected anosognosia for cognitive dysfunction in the AD population.

Caregiver Evaluation

Multiple regression and stepwise regression analyses were carried out using caregiver evaluation as a dependent variable and 16 independent demographic, behavioral, and clinical scores as potentially predictive variables. The results of the multiple regression analysis were highly significant ($F[17,172] = 11.09$, $R^2 = 0.52$, $P < 0.00001$). Caregiver evaluation (a high score corresponding to more severe cognitive impairment) was positively related to IADL score (global impairment in daily activities rated by the caregiver, $P < 0.00001$), patient's education ($P < 0.001$), NPI apathy score rated by the caregiver ($P < 0.01$), and the score on the Hamilton depression scale ($P < 0.04$). There was a negative correlation with semantic fluency performance ($P < 0.01$).

In the stepwise regression analysis, a model was significantly explained by six factors ($F[6,183] = 28.74$, $R^2 = 0.48$, $P < 0.001$). Predictive variables entered successively were the IADL score, semantic verbal fluency, education, score on the Hamilton depression scale, digit span (caregivers rated higher cognitive deficits in patients with poor digit span), and finally, NPI apathy score. The results demonstrated that the subjective evaluation by caregivers depended not only on reduced performances (impaired IADL, reduced verbal fluency, and poor digit span), but also on factors such as mood and behavior of AD patients.

Clinico-metabolic correlations of caregiver evaluations were sought by entering this score as variable of interest in a design matrix where age, MMSE score, and the predictive variables identified in the stepwise regression analysis were taken as confounding variables. As anticipated, there was no significant correlation because caregiver's evaluation provides a dementia score that is well explained by the confounding variables. To understand better this result, two secondary analyses were carried out where caregiver evaluations and MMSE scores were entered as variables of interest in two separate design matrices using age as the single confounding variable. The caregiver's score negatively correlated with metabolism in bilateral temporal and parietal associative cortices ($P < 0.05$, corrected), and less significantly ($P < 0.001$, uncorrected) with metabolism in the prefrontal cortex. The MMSE score showed an expected positive correlation with glucose metabolism in the same structures. Those analyses were not the main purpose of this report, but they provided arguments for the validity of our approach. Effectively, clinico-metabolic correlations showed that the caregiver's evaluation was related to metabolism in

TABLE II. Brain metabolic correlates of patients' self-cognitive evaluation

Region	Voxels	Coordinates (x, y, z)	Z score
Right parahippocampal cortex	156	22, −12, −30	4.36*
Left orbitofrontal cortex	381	−18, 36, −16	4.21*
Right gyrus rectus	236	12, 32, −16	3.84
Right insula	68	42, 6, 0	3.49
Left superior frontal sulcus	71	−18, 38, 44	3.47
Right middle temporal cortex	33	40, 4, −20	3.29

Coordinates (in mm) refer to Montreal Neurological Institute (MNI) standard stereotactical space in SPM.
Threshold $P < 0.001$ uncorrected.
* Threshold $P < 0.05$ corrected for multiple comparisons.

posterior and frontal associative areas, and such a finding was observed consistently with dementia scales [Salmon et al., 2005].

Patient Self-Evaluation of Cognitive Impairment

The results of the multiple regression analysis were highly significant ($F[17,172] = 4.56$, $R^2 = 0.31$, $P < 0.00001$). Self-evaluation scores of AD patients concerning their own cognitive impairment would be expected to be lower in patients with anosognosia. The score was positively related to rating on the Hamilton depression scale ($P < 0.0001$), so that patients with more symptoms of depression showed greater consciousness of their cognitive problems. It was also correlated with education ($P < 0.05$) and with delayed free recall at CVLT ($P < 0.05$), suggesting that a high level of education and better episodic memory were related to greater awareness of cognitive impairment. There was a negative association with semantic verbal fluency ($P < 0.05$) and phonological verbal fluency ($P < 0.05$), so that greater awareness of cognitive problems was observed in patients experiencing poorer language abilities. In the stepwise regression analysis, a model was significantly explained by five factors ($F[7,184] = 12.27$, $R^2 = 0.25$, $P < 0.000001$). Predictive variables entered successively were patient scores on the Hamilton depression scale, semantic fluency, delayed recall at CVLT, phonemic fluency, and education.

Clinico-metabolic correlations were obtained for self-evaluation of cognitive impairment by the patient, and the confounding variables entered in the design matrix were age, MMSE, and the predictive variables obtained in the stepwise regression analysis. Self-evaluation of AD patients (reflecting relative awareness of their cognitive impairment) was positively correlated to metabolism in right parahippocampal area and in left orbitofrontal region ($P < 0.05$, corrected), and ($P < 0.001$, uncorrected) in the right orbitofrontal cortex, the left superior frontal sulcus, the right middle insula and the right middle temporal gyrus (Table II; Fig. 1).

Another way to explore the component of anosognosia included in the patient's self assessment was to include caregiver evaluation as a confounding variable: this allowed to assess impaired judgment of the patient while taking into account his actual cognitive impairment (reported by the caregiver). In this analysis, the right parahippocampal area showed a significant positive correlation with patients' capacity to self-assess cognitive performance, whereas the correlation with orbitofrontal cortex and left superior frontal sulcus were less significant ($P < 0.001$, uncorrected; data not shown).

A possible confound in the analysis is that patients with very mild AD might give low evaluations of their cognitive deficits because they are effectively mildly impaired, and not because they are unaware of their impairments. We then excluded the less cognitively impaired patients (CDR score 0.5) and carried out a secondary analysis on 173 patients from our population with mild to moderate dementia (CDR scores 1 and 2): similar (less statistically significant) clinico-metabolic correlations were obtained (data not shown).

The Discrepancy Score

The results of the multiple regression analysis were highly significant ($F[17,172] = 5.55$, $R^2 = 0.35$, $P < 0.00001$). The dependent variable, the differential score of cognitive assessment between caregiver and patient, was high when patients showed more "anosognosia" (i.e., less awareness of cognitive dysfunction than that shown by their caregiver). It was significantly and positively related to the total IADL score, reflecting poor daily functioning ($P < 0.00005$), and to NPI apathy score ($P < 0.0005$). In the stepwise regression analysis, a model was significantly explained by three factors ($F[3,186] = 27.39$, multiple $R^2 = 0.30$, $P < 0.000001$). The IADL score was entered at the first step, then the NPI apathy score, and finally the CDR score (positively correlated with the anosognosia measurement).

For clinico-metabolic correlation, the discrepancy score was entered as the variable of interest in a design matrix where age, MMSE, IADL, NPI apathy, and CDR scores were confounding variables. There was a negative correlation between the discrepancy score and metabolism in left temporoparietal cortex ($P < 0.05$, corrected), and ($P < 0.001$, uncorrected) in right temporoparietal cortex, bilateral inferior temporal cortex, and left superior fontal sulcus (Table III; Fig. 2).

As mentioned above, one could argue that patients with very mild AD would give low evaluations of their cognitive deficits because they are effectively only mildly impaired, so that a low discrepancy score would not reflect anosognosia in this subgroup of patients. Although anosognosia was observed with discrepancy scores in very mild AD [Kalbe et al., 2005], we carried out a secondary analysis on 173 patients from our population with mild to moderate AD (CDR scores 1 and 2). In these patients, the discrepancy score was correlated with the same temporoparietal and inferior temporal cortices (data not shown).

DISCUSSION

Anosognosia is of major importance for clinicians concerned with dementia of the Alzheimer type. Most patients

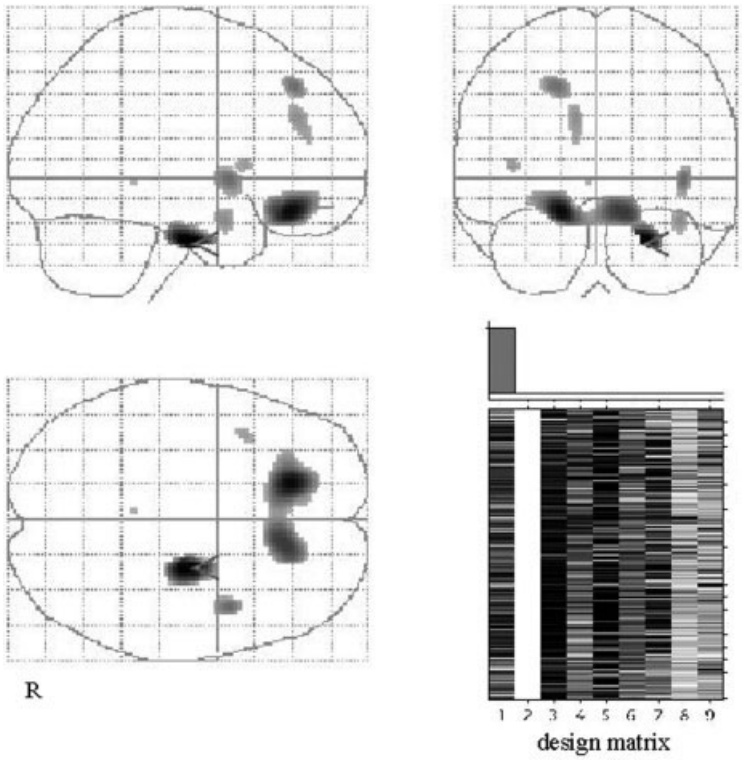

Figure 1.
Relationship between brain metabolism in our Alzheimer's disease population and self-cognitive assessment of patients (with multiple confounding variables). Statistical parametric maps ($P < 0.001$, uncorrected) are represented in a stereotactic space. R, right hemisphere.

at an early stage of AD tend to be aware of their cognitive deficits but may fail to appraise the true severity of their disease and its consequences in everyday life [Derouesne et al., 1999]. In patients with mild cognitive impairment but no dementia, a discrepancy score indicating greater informant than self-reported functional deficits might predict conversion to AD [Tabert et al., 2002].

Assessing anosognosia, however, is a complex task. The degree of awareness is variable for different domains of the dementia syndrome [Gil et al., 2001; Kalbe et al., 2005] and different measures of anosognosia may not have the same meaning. We used a research questionnaire to obtain evaluations of cognitive impairment from both patients and their caregivers. They all assessed cognitive impairments as mild on average, and the relatively small range of deficits required to use summed questionnaire scores in a large AD population for the analyses. We considered two measures of anosognosia for cognitive impairment, self-cognitive evaluation of AD patients and the discrepancy score between patient and caregiver evaluations. The regression analyses allowed us to assess precise relationships between our measures and demographic and clinical variables frequently related to anosognosia in the literature. To explore the neural substrate of our two measures of anosognosia, we capitalized on a large number of AD patients, recent programs for analysis of functional imaging, and confounding covariates corresponding to multiple clinical variables that influenced the measurements but did not explain anosognosia. Taking confounding variables into account was important because it was shown that lack of insight into memory impairment is related to but differs from the memory deficit itself [Agnew and Morris, 1998]. Different neural substrates specifically related to the "component of anosognosia" in our measures thus were shown by functional imaging. Accordingly, the contribution of multiple cognitive processes

TABLE III. Brain metabolic correlates of the discrepancy score

Area	Voxels	Coordinates (x, y, z)	Z score
Left temporoparietal junction	304	−56, −56, 32	4.27*
Right temporoparietal junction	154	66, −52, 30	3.86
Right inferior temporal gyrus	261	62, −14, −32	3.69
Left inferior temporal gyrus	130	−58, −12, −30	3.48
Left superior frontal sulcus	34	−26, 6, 64	3.47

Coordinates (in mm) refer to Montreal Neurological Institute (MNI) standard stereotactical space in SPM.
Threshold $P < 0.001$ uncorrected.
*Threshold $P < 0.05$ corrected for multiple comparisons.

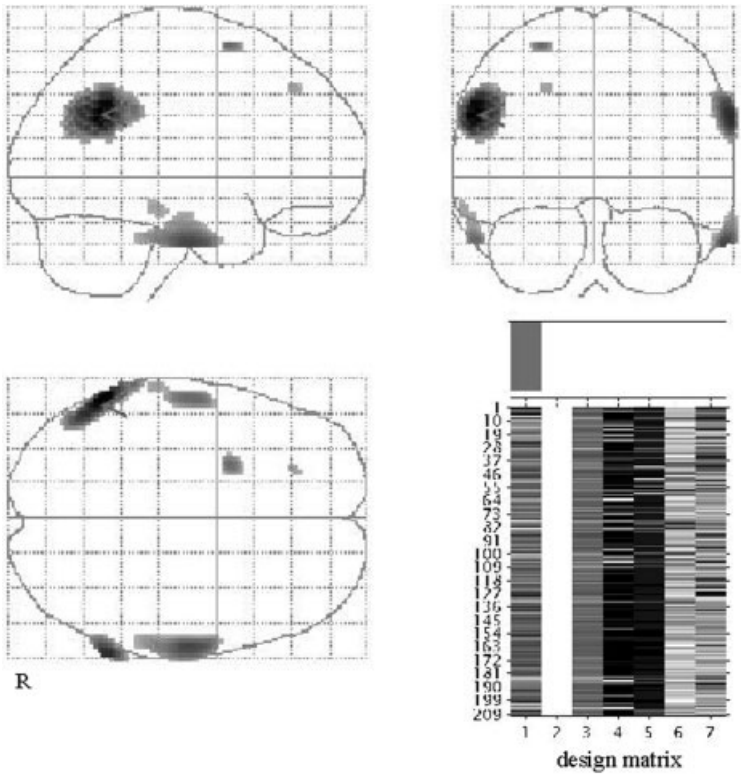

Figure 2.
Relationship between brain metabolism in our Alzheimer's disease patients and the discrepancy score (statistical parametric map; $P < 0.001$, uncorrected). R, right hemisphere.

was outlined clearly in previous models of anosognosia [Agnew and Morris, 1998]. As expected from the neuroimaging literature, the neural correlates of anosognosia in AD were located in frontal and parietal associative cortices.

The Neural Substrate of Anosognosia Measured by Patient Self-Assessment of Cognitive Impairment

Self-assessment of cognitive abilities by AD patients is a measure of anosognosia [Cummings et al., 1995]. The main drawback is that both AD patients with mild neuropsychological impairment and those with anosognosia would report mild cognitive difficulties. To avoid this problem, we introduced confounding variables such as dementia severity, objective episodic memory performance, or caregiver evaluations of the patient's cognitive impairment in the analysis of clinico-metabolic correlations; this allowed to demonstrate the presence of anosognosia in the self-cognitive evaluation of AD patients.

Impaired evaluative judgment about self cognitive capacities in AD patients was related to metabolic activity in the right parahippocampal and in the orbitofrontal cortex. Contrary to the literature, we did not observe a right predominance in frontal involvement, probably because we introduced a number of confounding variables in the analysis [Starkstein et al., 1995; Vogel et al., 2005]. There are different hypotheses explaining the integrated functioning of the hippocampal formation and the orbitofrontal area. Those regions, linked by the uncinate fasciculus, may be central for recollection of autobiographic information [Levine et al., 1998; Markowitsch, 1995]. Episodic memory performance was related to patient self-assessment in the regression analyses, and unawareness of the degree of cognitive deficit may be attributed partly to a failure to retrieve episodes of memory problems [Schacter, 1983]. Patient self-cognitive evaluation would not depend only on episodic memory in AD [Tulving, 1993], however, especially as episodic memory performance was introduced as a confounding variable in the correlation analysis. The principal task of our patients was not to retrieve episodic autobiographic information concerning their cognitive performance, but to provide self-evaluation about their cognitive impairment, which may depend on personal factual knowledge [Tulving, 1993]. Accordingly, the parahippocampal cortex was involved in semantic judgments [Bartha et al., 2003; Lekeu et al., 2003a; Luo and Niki, 2002], whereas a ventral limbic complex comprising the hippocampal formation and the orbitofrontal cortex has been proposed to intervene in the evaluation of conceptual information (such as questions on cognitive abil-

ities in our questionnaire) for their personal significance [Tucker et al., 1995].

Can we speculate as to the specific contribution of medial temporal and orbitofrontal structures? From a theoretical viewpoint, the hippocampal formation has been ascribed the role of a comparator [Gray, 1995; Wall and Messier, 2001] and comparator mechanisms were inserted in models of insight into cognitive ability [Agnew and Morris, 1998]. Medial temporal dysfunction thus might impair a comparison mechanism between current information and personal knowledge of cognitive abilities. In the literature, macaques with lesions of the caudal orbitofrontal cortex continue to respond to an object that is no longer associated with a reward [Butter et al., 1969; Jones and Mishkin, 1972; Rolls, 1996; Rosenkilde, 1979; Thorpe et al., 1983]. Based on this impaired association between stimuli and their rewarding value, it was suggested that such animals had "interoceptive agnosia" [Nauta, 1971]. The orbitofrontal cortex is also essential for sorting out mental associations that pertain to ongoing reality [Schnider et al., 2000b]. Failure to suppress currently irrelevant memory traces and to select temporally appropriate information was related to posterior orbitofrontal dysfunction in patients with confabulations [Schnider et al., 2000a] and in AD [Lekeu et al., 2003b]. According to this, impaired self-assessment of cognitive abilities in AD would be related to decreased ability to inhibit proactive interference of remote experiences, and to update associations between impaired cognitive capacities and their decreased qualitative value.

The Neural Correlates of the Discrepancy Score

A high discrepancy score means that an AD patient underestimates his cognitive difficulties compared to his caregiver's evaluation. Studies of the relationship between discrepancy score and brain activity measured with functional imaging have shown mainly a decrease of right frontal and parietal activity in AD patients with anosognosia [Derouesne et al., 1999; Leys et al., 1989; Reed et al., 1993; Starkstein et al., 1995]. The discrepancy score was inversely related to metabolism in temporoparietal junctions, and (to a lesser degree) in inferior temporal cortex and in left superior frontal sulcus in our population.

The temporoparietal junction found to be specifically related to anosognosia is part of the associative cortices related to dementia severity in AD [Salmon et al., 2005]. This explains the trend to greater anosognosia in more severely demented patients [McDaniel et al., 1995]. This also suggests that a relative anosognosia for cognitive impairment is a cardinal feature of AD [Kalbe et al., 2005; Tabert et al., 2002].

The regions related to the discrepancy score in AD were involved previously in self-referential processes and perspective taking. A recent meta-analysis emphasized superior frontal sulcus activation in self-referential tasks [Wicker et al., 2003]. Lesions of the temporoparietal junction were related to mirrored self-misidentification in demented patients [Breen et al., 2001]. In healthy subjects, bilateral activation of temporoparietal junctions was preferentially observed for retrieval of memories with personal relevance [Maguire and Mummery, 1999]. Activation of the temporoparietal junction was reported frequently in neuroimaging studies manipulating perspective taking [Decety and Sommerville, 2003; Ruby and Decety, 2004; Vogeley et al., 2001].

This suggests that dysfunction in the brain network related to the discrepancy score, comprising the temporoparietal junction and superior frontal sulcus, might reflect impairment of self referential processes and of the "third-person" knowledge that AD patients have of themselves [Agnew and Morris, 1998; Klein et al., 2003; Tulving, 1993].

CONCLUSION

This study was focused on two measures of anosognosia derived from a research questionnaire providing patient and caregiver assessments of multiple cognitive domains for our AD patients [Kalbe et al., 2005]. Regression analyses showed that both measures were related to demographic and clinical variables consistently described in the literature on anosognosia. Using a SPM matrix with appropriate confounding variables, the neural correlates of anosognosia derived from patient self-assessment of cognitive impairment comprised the posterior orbitofrontal cortex. Orbitofrontal lesions in AD would be related to impaired "present reality" monitoring, which may disturb judgment process and decision making. The neural substrate of the discrepancy score (difference of cognitive assessment between patient and caregiver) comprised temporoparietal cortices and involved in the self-versus-other comparative judgement required during perspective taking. Anosognosia measured by the discrepancy score might be interpreted as an impaired ability to see oneself with a third-person perspective (knowing how other people see ourselves). The frontal and temporoparietal regions highlighted in this study should be viewed as part of wider networks involved in awareness of cognitive deficits, and their impairment explains only some aspects of anosognosia in AD [Agnew and Morris, 1998].

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