Anosognosia in Alzheimer Disease: Disconnection between Memory and Self-related Brain Networks

Audrey Perrotin, PhD,[1,2,3,4] Béatrice Desgranges, PhD,[1,2,3,4] Brigitte Landeau, MSc,[1,2,3,4] Florence Mézenge, BA,[1,2,3,4] Renaud La Joie, PhD,[1,2,3,4] Stéphanie Egret, MSc,[1,2,3,4] Alice Pélerin, MSc,[1,2,3,5] Vincent de la Sayette, MD,[1,2,3,5] Francis Eustache, PhD,[1,2,3,4] and Gaël Chételat, PhD[1,2,3,4]

Objective: Impaired awareness is a common symptom in many mental disorders including Alzheimer disease (AD). This study aims at improving our understanding of the neural mechanisms underlying anosognosia of memory deficits in AD by combining measures of regional brain metabolism (resting state fluorodeoxyglucose positron emission tomography [FDG-PET]) and intrinsic connectivity (resting state functional magnetic resonance imaging [fMRI]).
Methods: Twenty-three patients diagnosed with probable AD based on clinical and biomarker data and 30 matched healthy control subjects were recruited in this study. An anosognosia index (difference between subjective and objective memory scores) was obtained in each participant. Resting state FDG-PET for glucose metabolism measurement and resting state fMRI for intrinsic connectivity measurement were also performed. AD and control groups were compared on behavioral data, and voxelwise correlations between anosognosia and neuroimaging data were conducted within the AD group.
Results: AD patients underestimated their memory deficits. Anosognosia in AD patients correlated with hypometabolism in orbitofrontal (OFC) and posterior cingulate (PCC) cortices. Using OFC and PCC as seed regions, intrinsic connectivity analyses in AD revealed a significant association between anosognosia and reduced intrinsic connectivity between these regions as well as with the medial temporal lobe.
Interpretation: Anosognosia in AD is due not only to functional changes within cortical midline structures involved in self-referential processes (OFC, PCC), but also to disconnection between these regions as well as with the medial temporal lobe. These findings suggest that the lack of awareness of memory deficits in AD results from a disruption of the communication within, but also between, the self-related and the memory-related brain networks.

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Anosognosia is defined as the impaired ability of patients with neurological disorders to recognize the presence or adequately appreciate the severity of their deficits.[1] In the present article, "anosognosia" will specifically refer to impaired awareness of memory deficits. Anosognosia is a common symptom in Alzheimer disease (AD)[2] and may already be present in early predementia stages, that is, in patients with mild cognitive impairment (MCI; see Roberts et al for review[3]). The presence or the degree of anosognosia, however, greatly varies from one patient to another, even at a similar stage of the disease.

The brain substrates of anosognosia are not fully understood. Previous neuroimaging studies using fluorodeoxyglucose positron emission tomography (FDG-PET) or single photon emission computed tomography (SPECT) have reported a significant relationship between

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Address correspondence to Dr Perrotin, Inserm-EPHE-Université de Caen Basse-Normandie U1077, GIP Cyceron, Bd Becquerel - BP 5229, 14074 CAEN Cedex 5, France. E-mail: audrey.perrotin@gmail.com

From the [1]INSERM (French National Institute of Health and Medical Research), Unit 1077, Caen, France; [2]University of Caen Lower Normandy, UMR-S1077, Caen, France; [3]EPHE (French Practical School of Higher Studies), UMR-S1077, Caen, France; [4]CHU (University Hospital Center) of Caen, Caen, France; and [5]Department of Neurology, CHU (University Hospital Center) of Caen, Caen, France

anosognosia in AD and hypometabolism or hypoperfusion in the prefrontal cortex (PFC), involving dorsolateral[4,5] and orbitofrontal regions,[6,7] as well as in the temporoparietal junction,[8,9] inferior parietal cortex,[10] posterior cingulate cortex (PCC), and precuneus.[11] Using functional magnetic resonance imaging (fMRI), Ries et al[12] reported a link between decreased activity in medial PFC and PCC during a self-appraisal task and impaired awareness of memory deficits in MCI patients compared to controls, suggesting a link between anosognosia and cortical midline structures. These cortical midline structures—namely the precuneus, the PCC, and the PFC—have been consistently shown to be involved in self-referential processes[13–15] (see Northoff et al for meta-analysis[16]).

However, cognitive deficits not only reflect the alteration of discrete brain regions but likely also result from the connectivity disruption between different brain regions, that is, network breakdown. Considering large-scale brain connectivity in addition to regional alterations would thus allow a more comprehensive assessment of the neural basis of anosognosia.[17] To our knowledge, only 1 previous report has assessed intrinsic connectivity correlates of anosognosia so far. In a mixed group of 12 MCI and AD patients,[18] anosognosia was related to decreased connectivity between the medial PFC, other PFC areas, and the posterior hippocampus. These preliminary results are in line with the proposal that anosognosia in AD would reflect a disconnection syndrome resulting from a disruption of the long-range transcortical temporofrontal circuit.[8] As a whole, the relationship between anosognosia and intrinsic connectivity has been only poorly investigated to date.

The objective of the present article is to further our understanding of the brain mechanisms underlying anosognosia in AD by using 2 complementary imaging modalities allowing us to unravel both the functional impairment of isolated brain regions (with resting state FDG-PET) and intrinsic connectivity disruption between brain regions (with resting state fMRI). We hypothesized that anosognosia in AD would reflect functional changes within specific regions involved in self-related processes and awareness, such as the cortical midline structures, together with changes in the connectivity between these structures and with brain areas involved in episodic memory processes such as the hippocampus. We expect that self-awareness of memory deficits would require effective communication between self- and memory-related brain regions.

To test this hypothesis, we recruited AD patients who underwent neuropsychological, FDG-PET, and resting state fMRI examinations. We first assessed the relationships between an anosognosia score and regional FDG uptake to identify the brain areas in which hypometabolism was specifically related to this deficit. We then assessed whether, over and above local alteration, the long-range intrinsic connectivity of these regions was related to anosognosia.

Subjects and Methods

Participants

Twenty-three patients with AD from the IMAP study (Caen, France[19,20]) were included in the present study. These patients were recruited from local memory clinics, and their clinical diagnosis of probable AD was made in accordance with the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association guidelines.[21] In addition, following the recent recommendations from the National Institute on Aging and Alzheimer's Association workgroup[22] for research studies, only patients with a high probability of AD etiology (ie, who have positive neuroimaging biomarkers for both Aβ deposition and neurodegeneration) were selected. The detailed procedure for biomarker-based dichotomization is described in La Joie et al,[19] which includes the same patients as the present study with 4 exceptions.

Thirty age-, education-, and sex-matched healthy control (HC) subjects were also included to be used as a reference group for clinical and neuropsychological data. They were recruited from the general population and included after clinical and neuropsychological examinations. They showed no history or clinical evidence of major neurological or psychiatric disorder, performed in the normal range in all neuropsychological tests, and had a Mini-Mental State Examination (MMSE) score $\geq$ 28. Demographic and clinical features of patients and controls are indicated in Table 1.

The study was approved by the local ethics committee and, after a complete description of the study was provided to the participants, written informed consent was obtained from all participants.

Neuropsychological and Behavioral Testing

OBJECTIVE MEMORY. Episodic memory was assessed with the Free and Cued Selective Reminding Test (RL/RI-16; French version[23]), a 16-word list verbal learning test. The 20-minute delayed free recall score was used as the objective episodic memory score.

SUBJECTIVE MEMORY. Self-reported memory decline was assessed with the Cognitive Difficulties Scale[24] (French version[25]). This scale is a 39-item questionnaire that requires participants to rate on a 5-point scale (from 0 = "never" to 4 = "very often") how frequently they experience particular cognitive difficulties in everyday life. The sum of the self-ratings from the 9 items referring to memory abilities was used as the subjective memory measure, with higher scores indicating greater perceived memory difficulties

TABLE 1. Demographic and Clinical Characteristics of Participants

Characteristic	HC, n = 30	AD, n = 23	Statistical Test	*p*
Age, mean yr (SD) [range]	68.37 (7.41) [54–81]	69.83 (9.63) [53–85]	$t = -0.62$	0.54
Gender, female, %	63.33	43.48	$\chi^2 = 2.07$	0.15
Education, mean yr (SD) [range]	12.00 (3.83) [7–20]	11.48 (3.70) [7–20]	$t = 0.50$	0.62
MMSE, mean (SD) [range]	29.17 (0.83) [28–30]	21.52 (4.62) [12–29]	$t = 8.90$	<0.001

AD = Alzheimer disease; HC = healthy controls; MMSE = Mini-Mental State Examination; SD = standard deviation.

MEMORY AWARENESS (ANOSOGNOSIA INDEX). An index of memory deficit awareness, called the delta score, was defined for each participant by calculating the difference between subjective and objective episodic memory scores (eg, Dalla Barba et al[26]). To allow comparison between both measures, (1) the subjective memory score was reversed so that, as for the objective memory score, a high score indicated a high self-rated level of performance; (2) the objective and the reversed subjective memory scores were standardized using the mean and standard deviation either from the HC group when intergroup comparisons were performed on the delta score, or from the AD group when intragroup comparisons or within-group correlations were performed; the former was mandatory to assess the degree of anosognosia in AD patients (compared to controls), whereas the later ensured that both objective and subjective standardized scores contributed equally to the delta score; and (3) the delta score corresponded to the subtraction of standardized objective from subjective memory scores, so that greater negative values indicated more severe anosognosia.

AFFECTIVE STATUS. The Montgomery–Asberg Depression Rating Scale (MADRS)[27] was used to measure the intensity of depressive affect, with higher scores indicating greater depressive symptoms. The total score on this scale was used as a nuisance variable in all analyses.

Brain Imaging

DATA ACQUISITION. Both structural and functional MRI scans were acquired as well as FDG-PET scans. Among the 23 AD patients, 2 patients did not have an FDG-PET scan, and 2 different patients did not have a resting state fMRI scan. All patients were scanned on the same MRI and PET scanners at the Cyceron Center (Caen, France), and neuropsychological and imaging assessments were performed within 1 month.

MRI Data. Both structural and functional MRI data were acquired on a 3T scanner (Philips Achieva, Eindhoven, the Netherlands). MRI acquisitions included: (1) a high-resolution T1-weighted anatomical volume using a 3-dimensional fast field echo sequence (3D-T1-FFE sagittal; repetition time [TR]/echo time [TE] = 20/4.6 milliseconds; flip angle = 10°; 180 slices; slice thickness = 1mm; field of view = 256 × 256mm^2; matrix = 256 × 256); (2) a high-resolution T2-weighted spin echo anatomical acquisition (2D-T2-SE sagittal); (3) a non–echo-planar imaging (EPI) T2* volume (2D-T2*-FFE axial); and (4) a resting state functional acquisition obtained using an interleaved 2D T2*SENSitivity Encoding (SENSE) EPI sequence designed to reduce geometrical distortions by using parallel imaging, shorter echo time, and smaller voxels (2D-T2*-FFE-EPI axial; SENSE factor = 2; TR/TE = 2,382/30 milliseconds; flip angle = 80°; 42 slices; slice thickness = 2.8mm; field of view = 224 × 224; in-plane resolution = 2.8 × 2.8mm^2; 280 volumes in 11.26 minutes; the first 6 volumes were discarded due to saturation effects). Before resting state fMRI scanning, participants were instructed to lie still within the scanner, keep their eyes closed without falling asleep, and let their thoughts go free.

PET Data. FDG-PET scans were acquired using a 64-slice Discovery Rx VCT PET-CT scanner (GE Healthcare Bio-Sciences, Piscataway, NJ) with resolution of 3.76 × 3.76 × 4.9mm^3 (field of view = 157mm). Patients were fasted for at least 6 hours before scanning. After a 30-minute resting period, ≈180MBq of FDG were intravenously injected as a bolus. A transmission scan was performed for attenuation correction, and then a 10-minute PET acquisition scan began 50 minutes postinjection. Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.2mm^3. FDG uptake was measured in standard resting conditions, with eyes closed, in a quiet and dark environment.

DATA PROCESSING AND ANALYSES. FDG-PET Data. The preprocessing of FDG-PET data included (1) voxel-wise correction for partial volume effects using T1-weighted MRI and the PMOD software (PMOD Technologies, Adliswil, Switzerland), (2) coregistration onto the corresponding T1-weighted MRI and spatial normalization to the Montreal Neurological Institute (MNI) space (resampled voxel size = 2 × 2 × 2mm) using the parameters estimated from the corresponding T1-weighted MRI using the Voxel-Based Morphometry 5.1 toolbox implemented in Statistical Parametric Mapping 5 (SPM5) software (Wellcome Trust Centre for Neuroimaging, London, UK), (3) quantitative scaling using the cerebellum gray matter as a reference to obtain standardized uptake value ratio images, (4) smoothing with a 12mm full-width half-maximum (FWHM) Gaussian kernel, and (5) masking to exclude non–gray-matter voxels. The resulting images were then used in the correlation analyses with the delta score.

TABLE 2. Neuropsychological Performances of HC and AD Participants

Test	HC, n = 30	AD, n = 23	Statistical Test	*p*
Objective memory, mean (SD) [range], delayed free recall; /16	12.60 (2.16) [8 to 16]	2.30 (1.79) [0 to 6]	$t = 18.48$	<0.001
Subjective memory, mean (SD) [range], memory self-reports; /36	10.63 (4.33) [2 to 19]	19.43 (6.17) [11 to 34]	$t = -6.10$	<0.001
Memory awareness, mean (SD) [range], delta score	0.00 (1.30) [−2.28 to 3.51]	−2.73 (1.71) [−5.75 to 0.49]	$t = 6.61$	<0.001

AD = Alzheimer disease; HC = healthy controls; SD = standard deviation.

Functional MRI. The preprocessing of resting state fMRI data is fully described in previous studies[20,28] with minor differences detailed below. Briefly, the procedure included (1) slice timing correction; (2) 3D motion correction; (3) coregistration of the mean functional image, non-EPI T2*-, T2-, and T1-weighted MRI images, and warping to the non-EPI T2* scan to reduce geometrical distortion effects[29]; (4) spatial normalization to the MNI space (resampled voxel size: 2 × 2 × 2 mm) using the parameters estimated from the corresponding T1-weighted MRI; (5) smoothing with a 4mm FWHM Gaussian kernel; and (6) temporal bandpass filter (0.01–0.08Hz) application to the images. The resulting images were then used in the intrinsic connectivity analyses, which included the following steps.

First, regions of interest were defined to be used as seeds for the intrinsic connectivity analyses. To assess the intrinsic connectivity of regions relevant to anosognosia in AD, we referred to the results of the correlation analysis between FDG-PET images and the delta score, selecting the significant clusters as seeds. The mean time course within each seed was extracted for each of the 21 AD patients. Then, intrinsic connectivity maps were created for each seed and for each patient. For this purpose, voxelwise positive correlations were calculated between each seed time course and the time course from all other gray matter voxels, including the 6 movement parameters generated from realignment as well as the time courses of the whole brain, the white matter, and the cerebrospinal fluid, and their derivatives as nuisance variables.[30] Each resulting correlation map was then standardized using a Fisher *r*-to-*z* transformation and smoothed with an 8mm FWHM Gaussian kernel. The resulting images were then used in correlation analyses with the delta score.

Statistical Analyses

NEUROPSYCHOLOGICAL DATA. Parametric statistics were applied after normal data distribution was confirmed within AD and HC groups using the Kolmogorov–Smirnov test. AD and HC group differences on neuropsychological continuous measures were assessed using independent sample *t* tests. The relationships of the delta score with demographic and neuropsychological data were assessed within the AD group using Pearson correlations. Statistical analyses on behavioral data were performed using STATISTICA software (v8.0; StatSoft, Tulsa, OK) with a threshold set at $p < 0.05$ for determining statistical significance.

BRAIN IMAGING DATA. All neuroimaging analyses were conducted within the AD patients. First, a voxelwise correlation analysis was performed between FDG-PET images and the delta score across AD patients using the Multiple Regression routine in SPM5 and with age, education, gender, and the MADRS as nuisance variables. The resulting clusters were used as seeds to compute individual intrinsic connectivity maps. These maps were in turn entered in a multiple regression analysis with the delta score across AD patients, controlling for age, education, gender, and the MADRS.

The Monte-Carlo simulation program (AFNI's 3dClustSim, http://afni.nimh.nih.gov) was used to determine the cluster extent allowing a statistical significance of $p < 0.05$ corrected for multiple comparisons. All analyses were repeated including the MMSE score as an additional nuisance variable. Moreover, to account for potential covariation of local PET versus connectivity measures, correlation analyses with metabolism were repeated correcting for connectivity and reversely.

Results

Neuropsychological Data

BETWEEN-GROUP COMPARISONS (AD VS HC). Neuropsychological performances of AD versus controls are presented in Table 2. The results showed a significant group effect on the objective and subjective memory scores as well as on the delta score. Relative to HC, AD patients had lower performances on the objective episodic memory test, higher ratings in the subjective memory test, and negative and lower delta scores, indicating underestimation of their memory deficits (ie, anosognosia). The distribution of the delta score within each group is shown in Figure 1.

WITHIN-GROUP CORRELATIONS (AD). No significant relationship was found between the delta score and age ($r = 0.02$, $p = 0.93$), education ($r = 0.05$, $p = 0.83$), gender ($r = -0.20$, $p = 0.35$), the MADRS score ($r = 0.24$, $p = 0.26$), or the MMSE score ($r = 0.30$, $p = 0.16$).

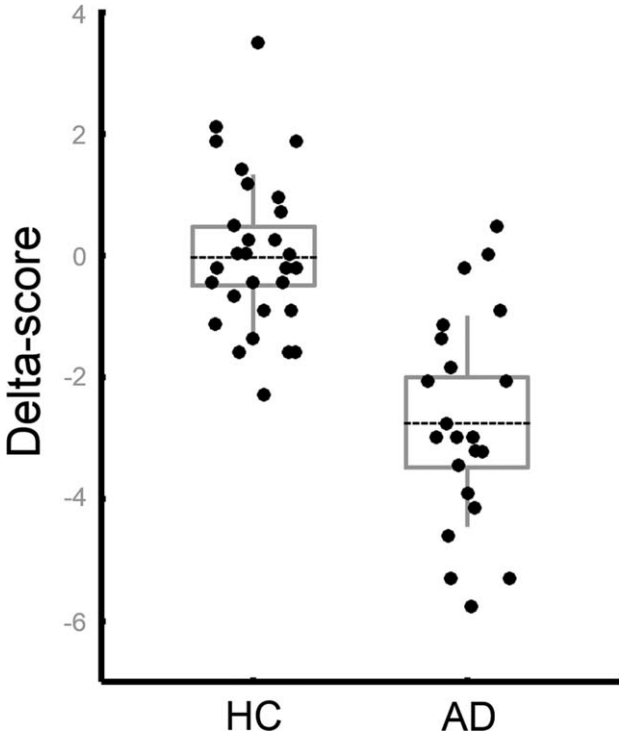

FIGURE 1: Delta score box plot within healthy control (HC; n = 30) and Alzheimer disease (AD; n = 23) groups.

Brain Imaging

RELATIONSHIPS BETWEEN GLUCOSE METABOLISM (FDG-PET) AND ANOSOGNOSIA IN AD. To yield an alpha of $p_{corrected} < 0.05$, which controls for false-positive rates, FDG-PET results were reported at a voxel-level threshold of $p < 0.005$ combined with a cluster extent of $k \geq 505$ voxels ($4{,}040mm^3$). The results are illustrated in Figure 2. Positive correlations between the delta score and FDG uptake (ie, greater anosognosia with lower glucose metabolism) in AD patients concerned the posterior and middle cingulate cortex (PCC), the precuneus, and the medial orbitofrontal cortex (OFC) including the rectus gyrus. The same findings were obtained including the MMSE as an additional nuisance variable, but the clusters were smaller. The seeds for the intrinsic connectivity analyses were obtained from this analysis but using a more stringent threshold ($p_{uncorrected} < 0.001$, $k \geq 200$ voxels) to limit their spatial extend. Two clusters were obtained, located in the PCC and the OFC (Fig 3A). Note that the correlations between the delta score and FDG uptake remained significant when controlling for the connectivity values in the same clusters.

RELATIONSHIPS BETWEEN INTRINSIC CONNECTIVITY AND ANOSOGNOSIA IN AD. These analyses aimed at identifying regions in which intrinsic connectivity with the PCC and the OFC was related with the delta score within the AD group. To yield an alpha of $p_{corrected} < 0.05$, intrinsic connectivity results were conducted among voxels positively correlated with the seed and reported at a voxel-level threshold of $p < 0.005$ and a cluster extent of $k \geq 142$ voxels ($1{,}136mm^3$) for PCC connectivity and of $k \geq 81$ voxels ($648mm^3$) for OFC connectivity. Figure 3 illustrates the results of the correlation analyses between intrinsic connectivity maps and the delta score. First, positive correlations were found between the delta score and the PCC connectivity with the left OFC including olfactory and rectus areas (see Fig 3C). Second, significant positive correlations between the delta score and the OFC connectivity were found with the left hippocampus and parahippocampal gyrus, and left medial OFC (see Fig 3B). When the MMSE was added as another nuisance variable, the results were similar. The correlations between the delta score and connectivity values remained significant after controlling for FDG uptake or gray matter volume within each corresponding seed, as well as controlling for the degree of trait anxiety or state anxiety at the time of the MRI.

Discussion

This study investigated the neural basis of anosognosia in AD patients with a clinical diagnosis confirmed by neuroimaging biomarkers, using 2 complementary neuroimaging approaches allowing the assessment of both regional metabolism and inter-regional intrinsic connectivity. Our results point to the involvement of anterior and posterior midline structures, known to have a role in awareness, and also to the disruption between these regions as well as with the medial temporal lobe. These findings provide empirical evidence supporting the hypothesis that impaired awareness of memory deficits at least partly results from a disconnection process in AD.[8] They further suggest that this disconnection operates within and between self-related and episodic memory-related brain regions.

Awareness of Memory Deficits in AD

Consistent with previous studies, we found that AD patients show impaired awareness of their memory deficits.[2] Thus, despite higher self-reported memory concern than controls, the subjective rating of their memory difficulties was still lower than their objective memory deficits as measured by an episodic memory test. We found that anosognosia severity was not significantly associated with demographic features (age, education, gender), depression (MADRS score), or global cognitive deficits (MMSE score) in our patient group.

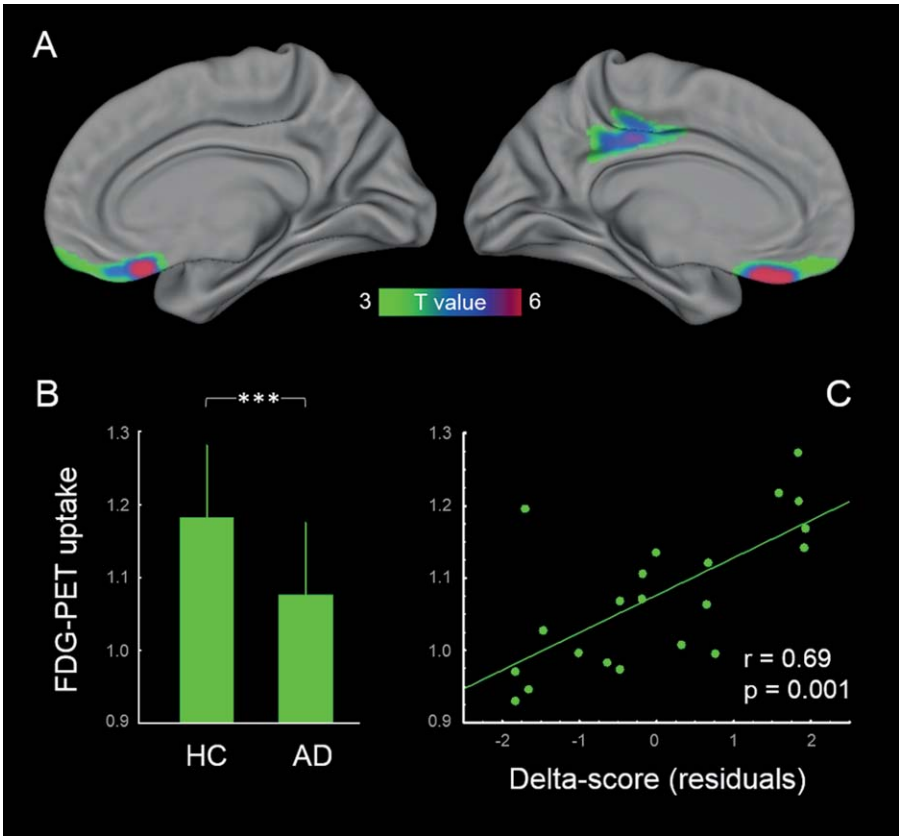

FIGURE 2: (A) Statistical parametric maps of the significant correlations between fluorodeoxyglucose (FDG) uptake and delta score in Alzheimer disease (AD) patients ($p < 0.005$, $k \geq 505$ voxels), controlling for age, education, gender, and Montgomery–Asberg Depression Rating Scale (MADRS). (B) Bar graph of the healthy control (HC) and AD group comparison on FDG uptake values in the significant clusters. *** = $p < 0.001$ PET = positron emission tomography. (C) Plot of the correlation between FDG uptake in the significant clusters and the delta score residuals (controlling for age, education, gender, and MADRS) in AD patients.

Brain Functioning Correlates of Impaired Awareness of Memory Deficits in AD

Two different but complementary functional imaging techniques have been used in this study to investigate anosognosia in AD. FDG-PET directly reflects neural activity through measurement of brain glucose metabolism consumption at rest; it has been used to provide an index of the functional integrity of brain regions. Resting state fMRI allows measurement of the blood oxygen level–dependent signals at rest, which indirectly reflect neural activity (itself mediated by regional tissue characteristics, metabolism, and cerebral blood flow and volume)[31] and has been used to provide an index of the intrinsic connectivity between brain regions.

GLUCOSE METABOLISM (FDG-PET). Increased severity of anosognosia in AD was found to be related to decreased glucose metabolism in the PCC and OFC, both hypometabolic in AD relative to HC. The orbitofrontal involvement is in line with an abundant literature pointing to the involvement of frontal areas in awareness or metacognitive processes,[2,32] and further confirms previous studies that have reported a link between anosognosia in AD and OFC dysfunction measured with either PET[9] or SPECT.[6,7,11] Comparatively, the involvement of the PCC has been less frequently reported in anosognosia in AD (SPECT[11]) but has been highlighted in self-appraisal fMRI studies of healthy adults. fMRI studies have repeatedly shown coactivation of medial PFC and PCC during self-appraisal tasks (for review see Johnson and Ries[17]), and decreased activity within these regions was related with a measure of anosognosia in MCI patients.[12] OFC and PCC thus appear as critical regions in the awareness of one's own memory. More generally, these cortical midline structures are known to be involved in self-referential processes (for meta-analysis see Northoff et al[16]). Particularly, OFC regions are known to be engaged in self-monitoring, self-representation, and self-judgment of cognitive abilities. The PCC would be involved in the retrieval and manipulation of autobiographical episodic memories.[33,34] Thus, our results provide additional evidence on the role of the dysfunction of these regions in the impairment of the awareness of memory deficits in AD.

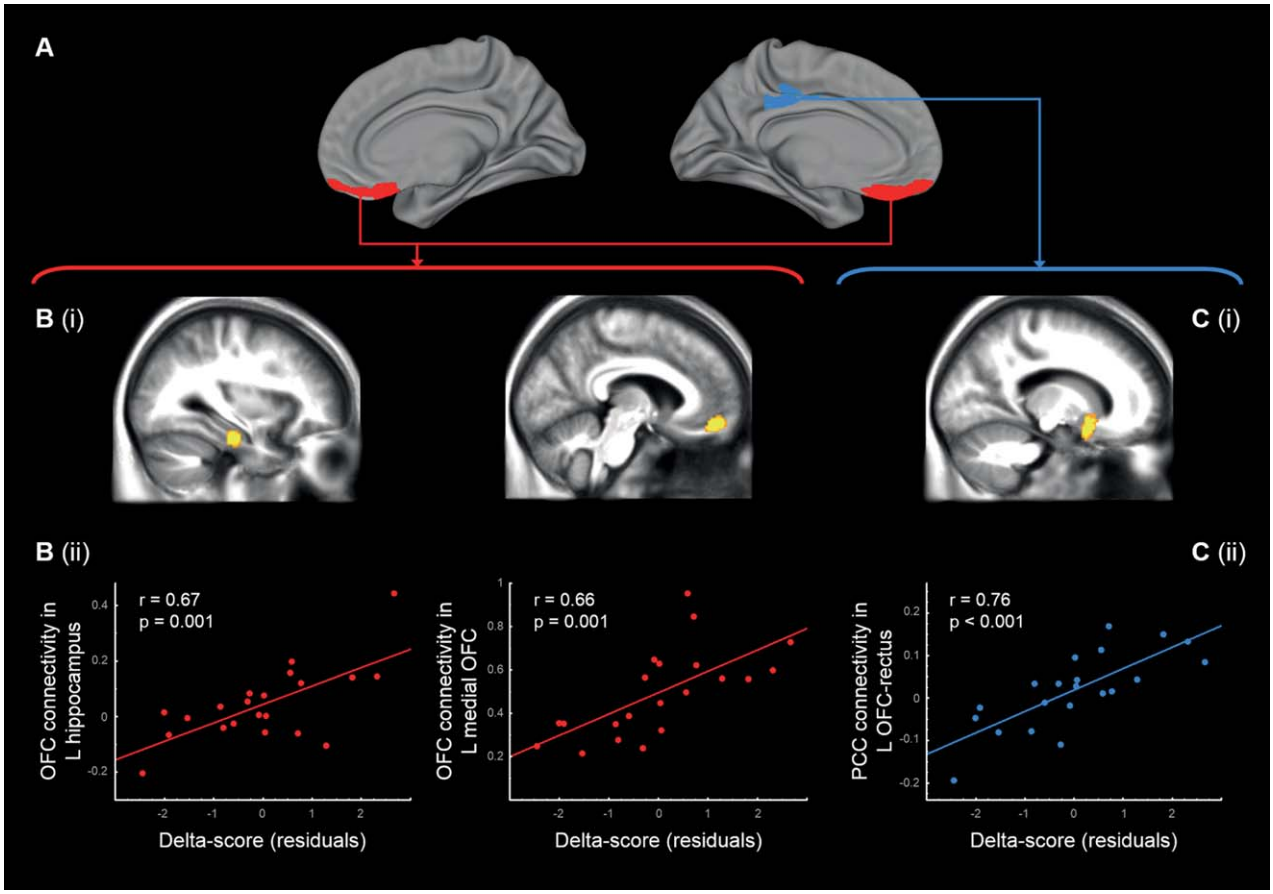

FIGURE 3: (A) Seeds used in the intrinsic connectivity analysis. (B, C) Significant correlations between the orbitofrontal cortex (OFC; B) and PCC posterior cingulate cortex (PCC; C) intrinsic connectivity maps and the delta score in Alzheimer disease patients ($p < 0.005$, $k \geq 142$ voxels for PCC connectivity and $k \geq 81$ voxels for OFC connectivity), controlling for age, education, gender, and Montgomery–Asberg Depression Rating Scale (MADR; i) and plot of the correlation between intrinsic connectivity in the significant clusters and the delta score residuals (controlling for age, education, gender, and MADRS; ii). L = left.

INTRINSIC CONNECTIVITY (RESTING STATE FMRI). Thanks to the use of resting state fMRI data, we further demonstrated that, in addition to impaired metabolism within OFC and PCC regions, anosognosia was also related with decreased intrinsic connectivity between these regions as well as with the medial temporal lobe. These findings are similar to those reported in Ries et al[18] showing a link between anosognosia and the connectivity between the medial PFC and the posterior hippocampus in a mixed group of 12 MCI and AD patients. Our results suggest that anosognosia is associated with a disruption of the connectivity between the PCC and the OFC, and between the OFC and the hippocampus. It can be hypothesized that this disconnection would reflect a disruption of the white matter fiber pathways that connect these structures, including the uncinate fasciculus,[35,36] which provides a direct hippocampofrontal route, and the cingulum bundle, which connects the OFC to the PCC, and the PCC to the hippocampus[37,38] (see also Villain et al[39]). Interestingly, the alteration of these pathways in AD has been largely documented in the literature (see Chua et al for review[40] and Sexton et al for meta-analysis[41]). Moreover, the brain areas unravel in the present study, that is, the OFC, PCC, and hippocampal regions also belong to the default mode network (DMN), a functional connectivity network that is active when individuals are engaged in internally focused tasks and known to be specifically sensitive to AD pathology.[42] Buckner et al[43] described this network as multiple interacting subsystems where the medial PFC, the PCC, and the medial temporal lobe are core regions that interact to process internal stimuli. Our findings suggest a role for the connectivity between DMN regions in memory capacity awareness, such that the disruption of the communication between these core regions in AD would underline anosognosia in these patients. More specifically, the OFC and PCC, on the one hand, are both known to be involved in self-related processes; on the other hand, the hippocampus is critical for episodic memory, which also implicates the PCC

especially for the retrieval of episodic and autobiographical memories.[34] Our results thus suggest that anosognosia in AD is associated with a disconnection both within and between self-related and memory-related networks. The disconnection within cortical midline structures (ie, between PCC and OFC) may reflect the alteration of internally oriented self-related processes.[44] As for the disconnection between the OFC and the hippocampus, it is consistent with theoretical accounts of anosognosia in AD that emphasize the association between self and memory.[45,46] In reference to anosognosia models,[45] it can be proposed that the disconnection both within, and between, self-related and memory-related regions may impair comparison and updating mechanisms between current information about memory functioning and self-knowledge about one's memory abilities. Considering the role of the OFC in monitoring, it is possible that disconnection from the hippocampus results in the inability of this region to assess with accuracy the memory inputs from the hippocampal regions[47] and/or to inhibit nonrelevant past memory experiences to select appropriate information about the present state of memory (impaired "present reality" monitoring[9]). Moreover, it may alter the comparison and mismatch detection between current and past autobiographical experiences, as well as the integration of memory failure into the self-database allowing the creation of an enduring awareness of one's memory abilities. Additionally, functional changes within the PCC may account for difficulties of AD patients in retrieving from autobiographical episodic memory previous experience of memory failure. As a whole, disruption of the connectivity both within and between memory-related and self-related brain areas in AD may result in the impairment of processes critical for the awareness of memory deficits that mutually reinforce each other and lead to anosognosia.

Some limitations of this work need to be acknowledged. First, the integrity of white matter fiber tracts has not been assessed in the present study. A work including diffusion tensor imaging in combination with resting state fMRI would be of great interest to further support our interpretation in terms of disconnection. Then, the method used to process resting state fMRI data in the present study could be criticized. First, a recent study showed that noise may be poorly controlled when the fMRI time series are bandpass-filtered but the nuisance variables regressed out in the intrinsic connectivity analyses are unfiltered.[48] Although widely used in the literature (eg, Fox et al[30]), the approach used in the present study could thus be improved. Second, our resting state fMRI data were smoothed twice, once with a light FWHM kernel before the intraindividual analyses to enhance the signal-to-noise ratio, and once with a larger FWHM kernel to reduce interindividual anatomical differences before interindividual connectivity analyses. Another criticism is related to the use of the delta score as an index of anosognosia, which may lack of ecological validity. It could be argued that questionnaires about everyday memory tasks may not be equivalent in levels of measurement to scores obtained on laboratory memory tests involving less familiar tasks. However, this method, used in several studies (eg, Dalla Barba et al,[26] Wagner et al[49]), presents the advantage of comparing the subjective report to an objective gold standard. This is not the case for the main alternative method, that is, comparing the patient's self-report to the informant's report, because judgment of the informant is not objective and may be biased by a number of factors (eg, the nature and frequency of the relationship with the patient, the potential motivation to make the patient look more or less impaired). Moreover, although the objective memory measure we used to compute the delta score did not show a floor effect, AD patients had low performances and 4 patients scored 0 on the delayed free recall test. This might have resulted in an overestimation of anosognosia in AD. Note however that all neuroimaging correlation analyses were repeated without these 4 patients and the results were less significant but similar (data not shown).

This is the first study to combine regional metabolism and inter-regional connectivity measurements to assess the neural substrates of anosognosia in a group of well-characterized AD patients. This association of 2 complementary approaches sheds light on our current understanding of the mechanisms of anosognosia. We showed that the loss of awareness of memory deficits in AD is not only due to the alteration of specific brain areas, but also to the breakdown of the connectivity within the self-related network as well as of the communication between this network and the memory-related brain network.

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Authorship

Study concept and design: G.C., B.D., F.E., A.Pe. Analysis and interpretation of data: A.Pe., G.C. Drafting of the manuscript: A.Pe., G.C.. Critical revision of the manuscript for important intellectual content: G.C., B.D., F.E., V.d.l.S., R.L.J. Statistical analysis: A.Pe., B.L., F.M. Administrative, technical, and material support: A.Pe., B.D., B.L., F.M., R.L.J., S.E., A.Pé, V.d.l.S., F.E., G.C.

Potential Conflicts of Interest

Nothing to report.

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