Received: 10 March 2019 | Revised: 7 August 2019 | Accepted: 8 August 2019

DOI: 10.1002/hbm.24775

RESEARCH ARTICLE

WILEY

Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease

Nicolas Antoine[1,2] | Mohamed A. Bahri[2] | Christine Bastin[2,3] | Fabienne Collette[2,3] | Christophe Phillips[2] | Evelyne Balteau[2] | Sarah Genon[2,4] | Eric Salmon[1,2,3]

[1]Memory Clinic, Department of Neurology, CHU of Liège, Liège, Belgium

[2]GIGA-Cyclotron Research Centre-IVI, University of Liège, Liège, Belgium

[3]Psychology and Neuroscience of Cognition, University of Liège, Liège, Belgium

[4]Institute of Neuroscience and Medicine, Brain and Behaviour (INM-7), Research Centre Jülich, Jülich, Germany

Correspondence
Eric Salmon, Cyclotron Research Centre, University of Liège, Quartier Agora, B30 Sart Tilman, Allée du 6 Août, 8, Liège 4000, Belgium.
Email: eric.salmon@uliege.be

Funding information
Fondation Roi Baudouin - Belgique, Grant/Award Number: Fonds Maria Elisa et Guillaume de Beys; Fonds De La Recherche Scientifique - FNRS; GE Healthcare, Grant/Award Number: Investigator Sponsored Study (ISS290); InterUniversity Attraction Pole, BELSPO, Grant/Award Number: IUAP 7/11; University of Liege, Grant/Award Number: Concerted Action 12/17-01

Abstract

Research on the neural correlates of anosognosia in Alzheimer's disease varied according to methods and objectives: they compared different measures, used diverse neuroimaging modalities, explored connectivity between brain networks, addressed the role of specific brain regions or tried to give support to theoretical models of unawareness. We used resting-state fMRI connectivity with two different seed regions and two measures of anosognosia in different patient samples to investigate consistent modifications of default mode subnetworks and we aligned the results with the Cognitive Awareness Model. In a first study, patients and their relatives were presented with the Memory Awareness Rating Scale. Anosognosia was measured as a patient-relative discrepancy score and connectivity was investigated with a parahippocampal seed. In a second study, anosognosia was measured in patients with brain amyloid (taken as a disease biomarker) by comparing self-reported rating with memory performance, and connectivity was examined with a hippocampal seed. In both studies, anosognosia was consistently related to disconnection within the medial temporal subsystem of the default mode network, subserving episodic memory processes. Importantly, scores were also related to disconnection between the medial temporal and both the core subsystem (participating to self-reflection) and the dorsomedial subsystem of the default mode network (the middle temporal gyrus that might subserve a personal database in the second study). We suggest that disparity in connectivity within and between subsystems of the default mode network may reflect impaired functioning of pathways in cognitive models of awareness.

KEYWORDS
Alzheimer's disease, anosognosia, connectivity, default mode network, memory, self

1 | INTRODUCTION

Anosognosia, a common symptom in Alzheimer's disease (AD), refers to an inaccurate assessment of personal limitations in daily activities. Dysfunctions are heterogeneous in AD and anosognosia may involve multiple facets of cognition, mood, behavior, and personality changes (Clare, Markova, Roth, & Morris, 2011). Existing studies are variable in terms of methods for assessing anosognosia (Clare, Markova, Verhey, & Kenny, 2005; Tondelli et al., 2018), domains of unawareness in AD (cognition, memory, behavior), disease stage, neuroimaging modality, and statistical analyses. Consequently, the neural correlates of anosognosia including frontal, temporal, parietal regions with

Nicolas Antoine and Mohamed A. Bahri are equally contributed to this study.

lateralization or not and midline structures (Sunderaraman & Cosentino, 2017; Zamboni & Wilcock, 2011) were relatively inconsistent across previous studies that used different approaches (Mimura & Yano, 2006; Salmon et al., 2006).

Current research on unawareness of cognitive impairment has adopted the clinical construct of anosognosia or/and the cognitive construct of metacognition (Clare et al., 2011; Sunderaraman & Cosentino, 2017). The complexity of the concept of self-(un)awareness is highlighted in different models. The Levels of Awareness model takes a biopsychosocial approach to conceptualize awareness phenomena (Clare et al., 2011). This framework is drawn upon the structure provided by models of consciousness and proposes that awareness consists of four interacting levels of increasing complexity: registration of information, monitoring of performance, evaluative judgments, and meta-representation of self. Each level may be increasingly influenced by characteristics of individual, contextual, and environmental factors. Available models specifying the cognitive processes and structures underpinning different aspects of awareness can be aligned with this framework. Such an influential model posits the existence of a Conscious Awareness System (CAS), located in the parietal regions, which receives information about the state of individual functional modules and passes the information on to an executive system (McGlynn & Schacter, 1989; Schachter, 1991). The model predicts that anosognosia for specific deficits may occur with disconnection of the CAS from individual modules, while more generalized anosognosia would occur with damage to the CAS or the executive system. The Cognitive Awareness Model (CAM) also provides a neurocognitive explanation of unawareness (Agnew & Morris, 1998; Morris & Mograbi, 2013). In this modular model, an autobiographical conceptual memory system, which represents a lifetime knowledge store, is connected to a personal database containing personal semantic representations. Learning about changes in one's abilities begins with performance on cognitive or social tasks. New information (processed in memory modules) is monitored by dedicated comparator mechanisms that contrast incoming information with representations stored in the personal database and the conceptual system. Each success or failure detected by performance monitoring leads to an evaluative process that may result in a change in self-appraisal. Then, a metacognitive awareness process emerges from reflective processes and evaluative judgements, informed by the conceptual system and the database and by the output of the comparators. Ultimately, a conscious metacognitive response is formulated. A mnemonic anosognosia occurs when there is a failure to update one's autobiographical knowledge regarding impaired cognitive abilities. Individuals with "mnemonic anosognosia" would detect cognitive failures, but cannot encode those failures into personal autobiographical memory. An executive anosognosia would arise when errors are not accounted for. Metacognitive awareness would be impaired by decreased connectivity between multiple modules, leading to generalized anosognosia. An important enrichment of the CAM is that emotional dysregulation may play a role in producing unawareness as failures would require an affective signature to motivate self-monitoring and evaluation (Rosen, 2011).

As memory deficit is the most consistent dysfunction in AD (McKhann et al., 2011), we focused on awareness of memory functioning, as assessed by the Memory Awareness Rating Scale (MARS), a tool that has been validated for AD (Clare, Wilson, Carter, Roth, & Hodges, 2002). In order to capture actual memory functioning via both a subjective and an objective approach, we used two different measures. In our first study, self-appraisal was contrasted to a relative's answers to the same questionnaire, a method called subjective rating discrepancy. The discrepancy was taken as a measure of unawareness of everyday memory functioning (Clare et al., 2011). However, some authors favor a discrepancy score between subjective self-rating ability and an objective test (the "subjective versus objective" discrepancy method) to assess anosognosia for memory impairment (Perrotin et al., 2015; Vannini et al., 2017). MARS questions were appropriately designed to match activities assessed with the Rivermead Behavioral Memory Test, in which ecologically valid tasks are analogous to memory skills required in everyday life (Wilson, Cockburn, & Baddeley, 1985). This "objective discrepancy score" was used in our second study, to explore consistency with Study 1 and with the literature.

In recent neuroimaging studies, unawareness of memory deficits assessed with objective discrepancy scores was related to hypometabolism in the posterior cingulate cortex (PCC) and disconnection between the medial temporal (MT) lobe and cortical midline structures in AD (Perrotin et al., 2015), or to decreased connectivity between the precuneus and the orbitofrontal cortex and inferior parietal lobe in mild cognitive impairment (Vannini et al., 2017). Most of those regions are part of the default mode network (DMN) (Zamboni & Wilcock, 2011), which comprises three functionally dissociable subsystems, including a dorsomedial prefrontal (dMPF) and a MT subsystem, which converge on a midline core system (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). Previous studies examining the neural correlates of anosognosia essentially reported correlations with regional brain structure or metabolism (Rosen et al., 2010; Starkstein, 2014; Tondelli et al., 2018).

Capitalizing on the interest in brain networks in neuropsychiatric diseases (Sha, Wager, Mechelli, & He, 2019) and the possible mapping of the components and pathways of models of unawarenes onto neuronal networks (Sunderaraman & Cosentino, 2017), the aim of the project was to test the idea that consistent relationships would be observed between two MARS discrepancy scores and dysfunction of DMN subnetworks. Specifically, we hypothesized that anosognosia for memory impairment would be related to disconnection within the MT subsystem of the DMN, which processes personal memories (Andrews-Hanna et al., 2010), and between the MT subsystem and cortical midline structures involved in self-evaluation (Northoff et al., 2006). We did not use a replication study design. We carried out two different studies with two samples of patients, connectivity analysis using resting fMRI and different seed regions in the MT subnetwork, and two standardized MARS assessments to estimate the consistency of patterns of neural dysfunction regardless of different types of anosognosia assessment.

2 | STUDY 1

2.1 | Materials and methods

2.1.1 | Participants

Thirty patients (21 women) with clinically probable AD took part in Study 1. To evidence their clinical profile, their demographic and clinical characteristics were compared to 19 (14 women) healthy older controls (HC). Patients were referred to the Memory Clinic of the University Hospital in Liege. The clinical diagnosis was based on recommendations in the literature (McKhann et al., 2011), after a clinical interview with the patient and a caregiver and general neurological and neuropsychological examinations. Hippocampal atrophy visually detected on a structural neuroimage was taken as biomarker of neurodegeneration (Scheltens et al., 1992). All patients had mild dementia with a typical amnestic presentation. The Mattis Dementia Rating Scale (MDRS) was used to assess the level of cognitive impairment (Mattis, 1976). None of the controls had a medical history of neurological or psychiatric conditions and they all scored in the normal range on the MDRS. For each participant, a close relative provided assessments of the participant's memory functioning using the MARS (Clare et al., 2002). Demographic and clinical features of the patients and HC are presented in Table 1. The University Hospital ethics committee approved the study and written informed consent was obtained from all participants.

2.1.2 | MARS

Patients and controls responded to the MARS––Functioning Scale. In this scale, sentences describing real-life situations that require memory abilities (e.g., "You have made an appointment. You need to remember to go along") are presented to the participant, who has to rate his/her likelihood of "success" on a five-point scale ranging from 0 (I am never able to do this) to 4 (I am always able to handle the situation). The relative assessed the participant's current abilities in each situation using the same scale. A discrepancy score was calculated for each question, corresponding to the difference between the patient's and the relative's rating divided by the mean of both evaluations. A total awareness score was calculated by averaging discrepancy scores across all questions (Clare, Whitaker, & Nelis, 2010).

TABLE 1 Demographic and neuropsychological data (Study 1)

	HC, *n* = 19	*Mild AD*, *n* = 30	*p*-value
Age, in years	73 (7)	78 (5)	.010
Gender, female, %	74	68	.800
Education, in years	12 (3)	10 (3)	.057
MDRS score, /144	138 (6)	123 (11)	<.001
MARS anosognosia score	−0.01 (0.14)	0.30 (0.39)	.003

Note: Values shown as mean (standard deviation). AD, Alzheimer's disease; HC, healthy controls; MARS, Memory Awareness Rating Scale; MDRS, Mattis Dementia Rating Scale. Statistical *t*-test and X^2 for gender.

2.1.3 | Neuroimaging acquisitions

For MRI, subjects were equipped with earplugs and their heads were stabilized with foam pads. A high-resolution T1-weighted anatomical image was acquired on a 3 T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil (three-dimensional modified driven equilibrium Fourier transform (MDEFT) sequence, TR 7.92 ms, TE 2.4 ms, TI 920 ms, FA 15°, FoV 256 × 224 × 176 mm^3, 1 mm isotropic spatial resolution; Deichmann, Schwarzbauer, & Turner, 2004). For resting-state fMRI time series, subjects were asked to relax, lie still in the scanner for 8 min and keep their eyes closed without falling asleep. Multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging (EPI) sequence using axial slice orientation and covering the whole-brain (32 slices, FoV 220 × 220 mm^2, voxel size 3.4 × 3.4 × 3.4 mm^3, 30% interslice gap, matrix size 64 × 64 × 32, TR 2130 ms, TE 40 ms, FA 90°, 250 volumes). The initial three volumes were discarded to avoid saturation effects.

2.1.4 | Data processing

For resting functional MRI, movement correction was performed using the realign function of SPM toolbox. Briefly, volumes were registered (rigid matching) to the mean image created after a first registration of all volumes to the first volume in the series, providing six movement parameters (three rotation and three translation). These parameters, plus their first-order temporal derivatives were regressed out from the time series signal. Moreover, with the aim of avoiding loss of data and/or subjects, we used the artifact detection tool to detect and model out artefacted volumes (ART; http://nitrc.org/projects/artifact_detect). Specifically, an image was defined as an outlier (artifact) image if the head displacement in *x*, *y*, or *z* direction was greater than .5 mm from the previous frame, if the rotational displacement was greater than .02 rad from the previous frame, or if the global mean intensity in the image was greater than three standard deviations from the mean image intensity for the entire resting scan. Outliers in the global mean signal intensity and motion were subsequently included as nuisance regressors (i.e., one regressor per outlier within the first-level general linear model). In this way, the temporal structure of the data was not disrupted. Further preprocessing steps included slice-time correction, co-registration of functional onto structural data, spatial normalization into the Montreal Neurological Institute (MNI) space (voxel size 2.0 × 2.0 × 2.0 mm^3), and smoothing with a Gaussian isotropic kernel (8 mm FWHM). Spatial normalization followed a Diffeomorphic Anatomical Registration Through an Exponentiated Lie algebra (DARTEL) approach based on the segmented T1-weighted MRI. Functional connectivity analyses adopted a seed-driven approach using the functional connectivity toolbox CONN v16.a (http://nitric.org/projects/conn/; Whitfield-Gabrieli & Nieto-Castanon, 2012). Noise reduction, white matter and cerebrospinal fluid signal removal and the temporal band-pass filtering (0.01–0.1 Hz) were done according the procedures described elsewhere (Kurth, Moyse, Bahri, Salmon, &

Bastin, 2015). Outliers in the global mean signal intensity and motion were subsequently included as nuisance regressors during the functional analysis. We chose a strategic node of the MT subsystem of the DMN as a seed (Chavoix & Insausti, 2017). The choice was influenced by the bottom-up design of the CAM, where medial temporal regions were the most obvious regions underlying episodic memory (see Figure 3 for a simplified model). The posterior parahippocampal cortex (PHC) is a primary hub modulating functional connectivity between posterior DMN nodes and the hippocampus (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008), making it a region of choice to confirm disconnection in AD. Bilateral seeds were defined as 3-mm-radius spheres around the PHC peak coordinates, (x = −26, y = −40, z = −12) and (x = 26, y = −40, z = −12), respectively (Andrews-Hanna et al., 2010; Kahn et al., 2008). The connectivity maps (beta-maps) were used for correlation with the anosognosia score within the AD group. Age, gender, education, and disease severity were entered as nuisance covariates. A separate analysis was performed to test for the significance of possible hemispheric laterality.

2.1.5 | Statistical analysis

Data were normally distributed and we used two-sample t-test (assuming independent and nonequal variance) to compare groups, and Pearson correlations to assess the relationships between MARS, MDRS and demographic data. The significance threshold was set at $p < .05$.

For MRI data, a voxel-level threshold was set at $p < .001$ uncorrected. Thresholded maps were then subject to a whole-brain correction criterion based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false positive rates (AFNI's 3dClustSim, http://afni.nimh.nih.gov). After 10,000 iterations, the minimum cluster size threshold $k > 134$ that yielded a cluster-level false positive rate (alpha) of 5% was estimated and applied to the statistical maps. Only clusters with a $p < .05$ after familywise error rate (FWER) correction were considered significant.

2.2 | Results

The unawareness (MARS) score was significantly higher in patients with mild AD than in controls, indicating that patients underestimated their memory impairment. In patients, no correlations were found between neuropsychological scores and demographic data. Furthermore, there was no significant correlation between MDRS and MARS scores in this sample of patients with mild dementia (r = −.03, p = .87).

In the resting-state fMRI results, significant correlations were found between anosognosia in AD and decreased connectivity between the bilateral posterior PHC and bilateral posterior inferior parietal lobe (k = 927 voxels on right IPL, and k = 310 voxels on left IPL), vPCC (k = 652 voxels) and right middle temporal gyrus (k = 390 voxels, $p_{FWE\text{-}corr.} < .001$; Figure 1). Strikingly, disconnection involved different DMN subsystems. No significant hemisphere-related differences were observed.

3 | STUDY 2

3.1 | Materials and methods

3.1.1 | Participants

Sixty-eight individuals (38 women) were included in the study, comprising 53 patients (27 women) with mild cognitive impairment (MCI-AD) or mild to moderate clinical AD and 15 HC (11 women) to compare demographic and clinical characteristics. MCI-AD and AD participants had positive amyloid-PET measured with [18F] flutemetamol (Nelissen et al., 2009). None of the controls had a medical history of neurological or psychiatric conditions. HC scored within the normal range on the MDRS and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and their clinical dementia rating (CDR) score was 0 (Morris, 1993). Patients were referred to the Memory Clinic of the University Hospital in Liege. Subjects with MCI had MMSE scores between 24 and 29, had memory complaints verified by an informant, documented abnormal memory function on neuropsychological examination, had a CDR score of 0.5, and general cognition and function assessed with the Instrumental Activities of Daily Living four-item scale (IADL) in the normal range (Lawton & Brody, 1969; Winblad et al., 2004). AD met the published criteria for probable AD with typical amnestic presentation (McKhann et al., 2011), with a CDR score of 1 or 2 and an IADL score between 5 and 13. Demographic and clinical features of patients and controls are described in Table 2 (with additional variables compared to study (a) MCI and AD samples had similar brain amyloid standardized uptake value ratios (Thurfjell et al., 2014) and were considered as a continuum of AD pathology, with participants presenting a continuum of anosognosia for memory impairment (Galeone, Pappalardo, Chieffi, Iavarone, & Carlomagno, 2011). The University Hospital ethics committee approved the study (EudraCT was BE2012-004462-18), and written informed consent was obtained from all participants.

3.1.2 | Memory Awareness Rating Scale––Adapted (MARSA)

The MARS Functioning scale addressed memory functioning in 13 everyday life situations that are equivalent to the analogous tasks incorporated in the Rivermead Behavioral Memory Test, such as remembering a name, remembering a new item, recognizing faces that have been shown before, retracing a short route, and delivering a message (Clare et al., 2002). Discrepancy scores were calculated by subtracting an adjusted (to the MARS) Rivermead Behavioral Memory Test standardized value from the participant's self-rating value, divided by the mean of both values for a given question. A total awareness score was calculated by averaging these discrepancy scores across all questions.

3.1.3 | Neuroimaging acquisitions

For the MRI scans, conditions of acquisition were similar to those of Study 1. The T1-weighted anatomical image was acquired using

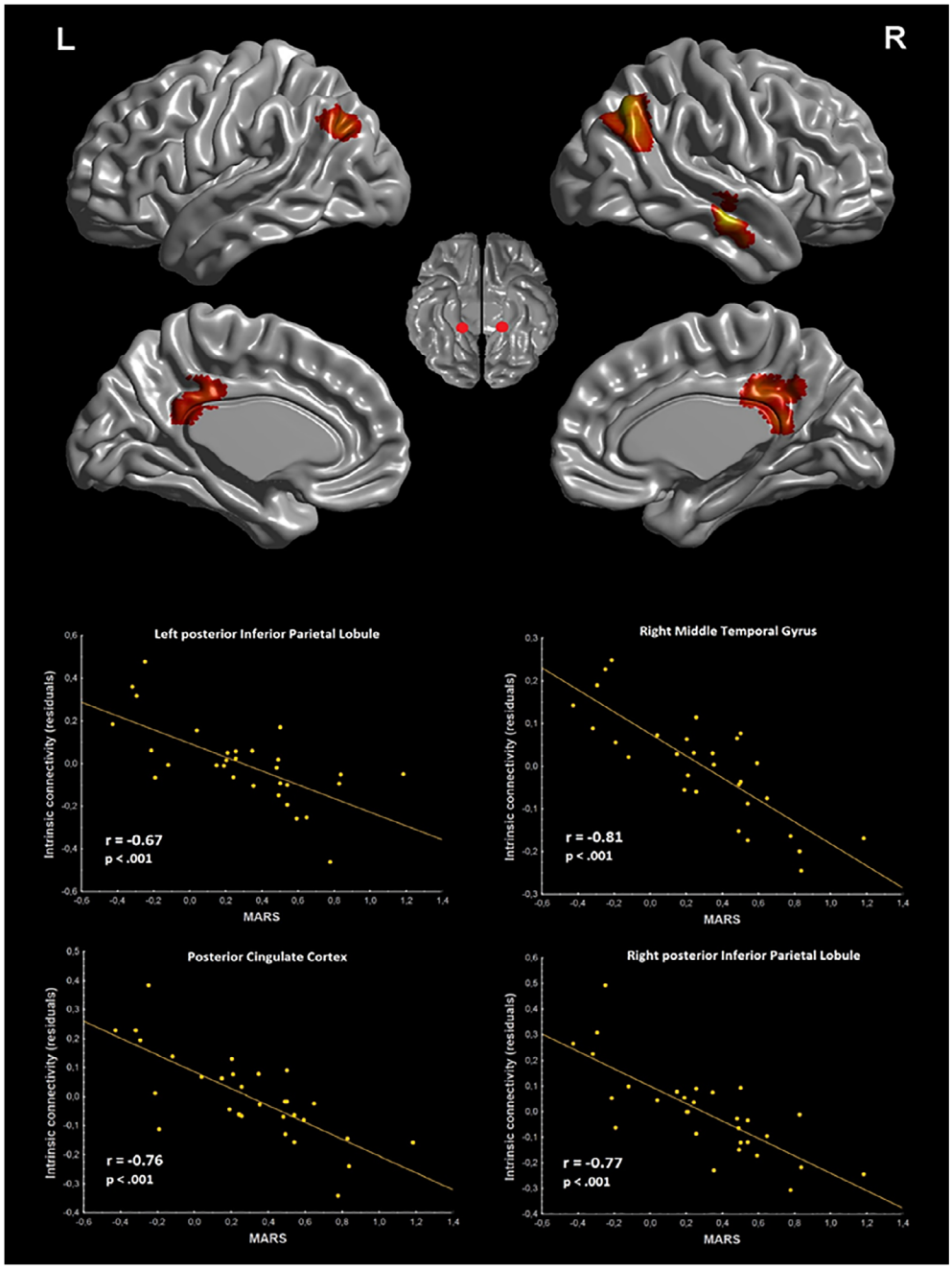

FIGURE 1 Voxel-wise regression analysis between memory awareness rating scale (MARS) anosognosia scores and parahippocampal cortex (PHC) seed-based connectivity maps in Alzheimer's patients. The cluster obtained in the CONN analysis was used as a mask to extract values used in the graph (mean value over the cluster) [Color figure can be viewed at wileyonlinelibrary.com]

T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR 2010 ms, TE 4.37 ms, TI 1100 ms, FA 8°, FoV 230 × 173 mm^2, 0.9 mm isotropic voxel size). The resting-state fMRI time series were acquired using a similar EPI sequence as in the first study (34 slices, FoV = 192 × 192 mm^2, voxel size 3 × 3 × 3 mm^3, 25% interslice gap, matrix size 64 × 64 × 34, TR = 2040 ms, TE = 30 ms, FA = 90°, 250 volumes). Immediately after the EPI session, a gradient-recalled sequence was applied to acquire two complex images with different echo times (TE = 4.92 and 7.38 ms, respectively) and generate field maps for EPI distortion correction. The other acquisition parameters were TR = 367 ms, FoV = 230 × 230 mm^2, 64 × 64 matrix, 34 transverse slices (3 mm thickness, 25% interslice gap), flip angle = 90°, bandwidth = 260 Hz/pixel.

3.1.4 | Data processing

For resting-state fMRI, in addition to the preprocessing described in Study 1, EPI time series were corrected for motion and distortion using the Realign and Unwarp procedure, together with the FieldMap toolbox available with SPM12.

3.1.5 | Statistical analysis

The experimental neuropsychological examination included the MDRS, MARSA and Rey Auditory Verbal Learning Task (Rey, 1964), as episodic memory test (RAVLT total and delayed recall). The hospital anxiety and depression scale (HADS; Zigmond & Snaith, 1983) total

TABLE 2 Demographic and behavioral data (Study 2)

	HC n = 15	*Aβ + AD n* = 53	*p*-value
Age, in years	72.7 (7.6)	75.2 (6.5)	.33
Gender, female, %	73	52	.15
Education, in years	13.9 (2.8)	11.5 (3.3)	.019
MMSE, /30	29.6 (0.6)	23.3 (4.1)	<.0001
IADL, /16	4.0 (0.0)	7.0 (2.7)	N/A
CDR	0	1.1 (0.6)	N/A
HAD, /42	8.6 (4.5)	9.3 (5.4)	.97
DRS (Mattis), /144	138.1 (4.1)	120.1 (12.3)	<.0001
RAVLT (total recall), /75	46.1 (12.7)	25.1 (11.3)	<.0001
RAVLT (delayed recall), /15	10.8 (2.9)	3.7 (4.1)	<.0001
RBMT, /52	43.3 (6.9)	16.2 (12.9)	<.0001
MARSA anosognosia score	−0.03 (0.12)	0.47 (0.37)	<.0001

Note: Values as mean (standard deviation). AD, Alzheimer's disease; CDR, clinical dementia rating; DRS, dementia rating scale; HAD, hospital anxiety and depression scale; HC, healthy control; MARSA, memory awareness rating scale adapted; MMSE, Mini Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test. Mann–Whitney *U* tests and Chi squared test for gender.

score was used as a nuisance variable in all analyses. For statistical analyses of demographic and behavioral data, we consistently used nonparametric methods to account for skewed distributions in some variables. The Mann–Whitney *U* test was used to compare two groups on continuous variables while chi-square tests were performed to examine group distribution differences on categorical variables. We used Spearman correlations to evaluate associations between anosognosia, global cognition, RAVLT total and delayed recall and demographic data. The statistical threshold was set at $p < .005$ (with Bonferroni correction).

To analyze resting-state functional connectivity, we used the seed-based approach as in Study 1. To search for consistency of results regardless of study design, we tested another seed in the MT subsystem of the DMN, located within the hippocampal body (bilateral 3-mm-radius sphere around the coordinates $x = 24$, $y = -14$, $z = -20$ and $x = -24$, $y = -14$, $z = -20$). This region is strongly correlated with the retrosplenial cortex extending into the PCC, IPL, and posterior PHC (Kahn et al., 2008), and is interesting for further exploring the relationship between possible MT subsystem disconnection in the DMN and anosognosia for memory impairment. Age, gender, education, and anxiety and depression score were entered as nuisance covariates. The analysis was also repeated including the RAVLT delayed recall scores as additional nuisance variables. RAVLT scores were used as confounding variable (rather than MDRS score) since they provide a more precise estimation of memory deficits interacting with anosognosia for memory impairment than the broad dementia rating. One-tailed *t*-test was used to test our a priori hypothesis of a negative correlation. The resulting set of voxel values was first thresholded at $p < .001$ (uncorrected) with the minimum cluster size threshold that yielded an alpha of 5% for false positive rate based on Monte Carlo simulations. Only clusters with a $p < .05$ after FWER correction were considered significant.

As a complementary analysis, we also performed the analysis with the same seed region as in Study 1 (but with the subjective vs. objective anosognosia score).

3.2 | Results

Neuropsychological data for patients with AD and HC are reported in Table 2. Compared to controls, patients had significantly higher MARSA scores ($p < .001$), indicating underestimation of their memory deficits. Within the AD group, no significant relationship was found between the MARSA score and age, gender, education, or the anxiety/depression score. However, a significant negative correlation was found between MARSA score and MDRS ($r = -.64$; $p < .001$), RAVLT total recall ($r = -.55$; $p < .001$) and delayed recall ($r = -.63$; $p < .001$) scores.

For resting-state fMRI, Figure 2 illustrates a significant correlation between the MARSA score and the degree of disconnection between the hippocampus and the retrosplenial cortex extending to the vPCC ($p_{FWE\text{-}corr.} < .05$, $k = 1{,}243$ voxels) and the right posterior IPL ($p_{FWE\text{-}corr.} < .05$, $k = 174$ voxels). We also found a significant correlation with decreased connectivity between the hippocampus and the ventromedial prefrontal cortex or vMPFC ($p_{FWE\text{-}corr.} < .05$, $k = 163$ voxels). Results were maintained when MDRS and RAVLT scores were added as nuisance variables. The same analysis using PHC coordinates of Study 1 as seed region did not provide any statistically significant results.

4 | DISCUSSION

This report focused on neural connectivity related to unawareness of memory impairment in participants with AD, based on two resting fMRI neuroimaging studies that differed according to seed regions in the MT subsystem of the DMN, measures of unawareness and samples of patients. The two studies yielded complementary, consistent results, which are discussed jointly below, in light of the multiple cognitive processes, neuropsychological hypotheses and brain interactions that would explain anosognosia according to the CAM (Morris & Mograbi, 2013).

4.1 | Anosognosia-related disruptions of brain intrinsic connectivity

In Study 1, we demonstrated that anosognosia for memory deficits was related to decreased intrinsic connectivity between the PHC and the posterior IPL, retrosplenial/vPCC, and right middle temporal gyrus. Among these regions, the vPCC and middle temporal cortex belong to the core and the dorsomedial subsystem of the DMN, respectively. In Study 2, we also showed that anosognosia for memory deficits in AD was related to decreased connectivity between the hippocampal body and midline structures such as the vPCC and vMPFC. The alteration

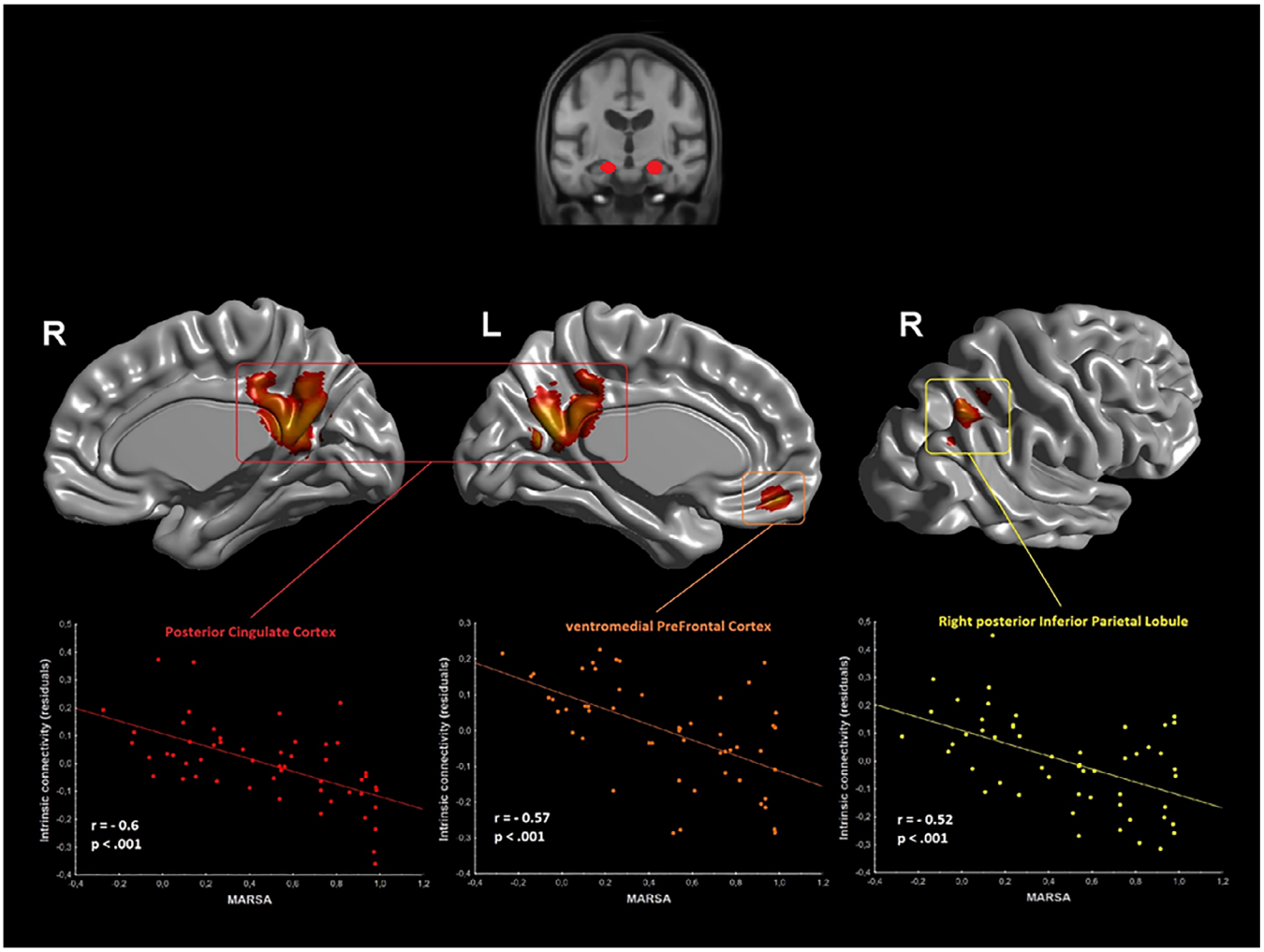

FIGURE 2 Voxel-wise regression analysis between Memory Awareness Rating Scale—Adapted (MARSA) anosognosia scores and hippocampal seed-based connectivity maps in Alzheimer's patients. The cluster obtained in the CONN analysis was used as a mask to extract values used in the graph (mean value over the cluster) [Color figure can be viewed at wileyonlinelibrary.com]

of functional connectivity also affected the right posterior IPL. Our data extend previous findings of association between anosognosia for memory deficits and reduced connectivity between core DMN regions and either the MT in AD (Perrotin et al., 2015; Ries et al., 2012), or the IPL in MCI (Vannini et al., 2017). More specifically, the results are consistent in our two studies and support the idea that disconnection *within* the MT subsystem and *between* the MT and other DMN subsystems are related to mechanisms that are central to unawareness in AD independently of the method and the population used to evidence it. In light of the CAM, this suggests that anosognosia is related to disconnection between the components of episodic memory, personal memory, and self-evaluation that involve distinct DMN subnetworks.

4.2 | An hypothetical interpretation of the data based on the CAM

Our seed regions in connectivity analyses were purposefully located in MT structures. Alzheimer's pathology primarily affects the MT subsystem, which leads to an episodic autobiographical memory dysfunction (Addis, Wong, & Schacter, 2007). Hippocampal structures participate to our ability to "re-experience" episodic events (Byrne, Becker, & Burgess, 2007) and lack of episodic memory has been proposed to participate to unawareness of memory impairment in the CAM. Accordingly, atrophy in hippocampal structures was recently shown to play a key role in anosognosia (Tondelli et al., 2018). In Figure 3, we superimposed the DMN regions that were disconnected onto a simplified representation of the CAM.

The middle temporal gyrus (part of the dorsomedial subsystem) plays a key role in conceptual processing and may store semantic knowledge of life items and other concrete conceptual information (Binder & Desai, 2011). Most imaging studies of autobiographical memory reported activation in the middle temporal gyrus, which could be a key region for the personal database in the CAM (Svoboda, McKinnon, & Levine, 2006). Dysfunctional connectivity between the middle temporal gyrus and MT structures had already been reported in patients who presented unawareness for memory deficit (Berlingeri et al., 2015). Accordingly, anosognosia may be related to a lack of

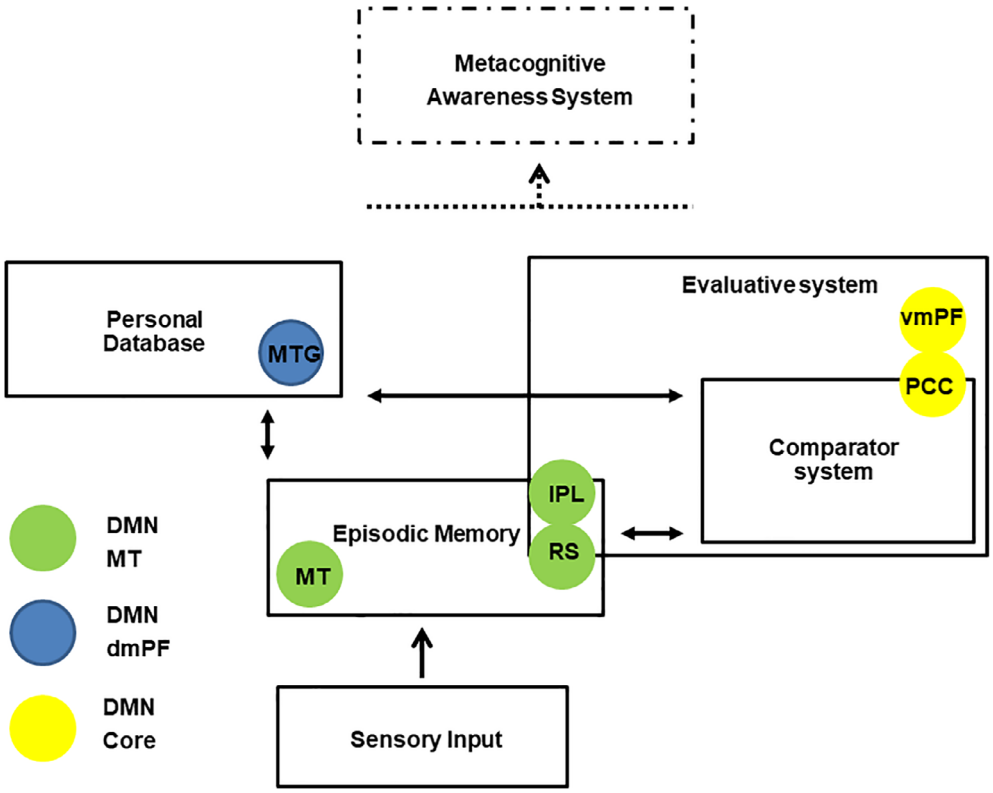

FIGURE 3 A simplified representation of the cognitive awareness model. Brain regions in the DMN showing disconnection with our medial temporal seed regions are superimposed on the model. dmPF, dorsomedial prefrontal; IPL, inferior parietal cortex; MT, medial temporal; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; RS, retrosplenial cortex; vmPF, ventromedial prefrontal cortex [Color figure can be viewed at wileyonlinelibrary.com]

integration between the lateral temporal cortex (a key region for the personal database) and the MT subsystem in processing novel personal information. In AD, patients fail to recalibrate knowledge of their own abilities in their personal database via ineffectively encoded episodic experiences and rely on a remote, currently inaccurate, sense of their own ability to judge their expected capacity (Morris & Mograbi, 2013). Such an inability to mentally travel in time participates in autonoetic consciousness impairment (Tulving, 2002), and gradually leads to a decreased sense of self-continuity over time (Weiler, Northoff, Damasceno, & Balthazar, 2016). Deprived of recent autobiographical episodes, patients will gradually switch to a more conceptual interpretation of personal experiences using semantic memory (Martinelli, Anssens, Sperduti, & Piolino, 2013) and their imperfectly updated personal database (Morris & Mograbi, 2013).

Previous studies had reported a relationship between anosognosia in AD or MCI and posterior midline cortex dysfunction (Gerretsen et al., 2017; Perrotin et al., 2015; Therriault et al., 2018; Vannini et al., 2017). Our findings point to the involvement of the ventral PCC and the retrosplenial cortex. The retrosplenial cortex is part of the DMN's MT subsystem and the vPCC is part of the midline core network (Andrews-Hanna et al., 2010). Both regions are predominantly involved in supporting various aspects of internally directed thought (Andrews-Hanna et al., 2010), including episodic memory retrieval (Vann, Aggleton, & Maguire, 2009). The vPCC is also involved in self-relevance assessment and self-reflection (Vogt, Vogt, & Laureys, 2006). Moreover, in a meta-analysis of functional neuroimaging studies focusing on semantic processing, Binder found that the PCC was one of the most consistently activated regions (Binder & Desai, 2011). In keeping with those data, it was proposed that the PCC acts as an interface between the semantic retrieval and episodic encoding systems (Bird, Keidel, Ing, Horner, & Burgess, 2015). In other words, the PCC integrates incoming new episodic experiences with existing knowledge to create a coherent representation of events, resulting in a semanticized form of memory that is resistant to forgetting (Bird et al., 2015). In the CAM, the PCC might be involved in conscious maintenance and manipulation of new information and in self-knowledge retrieval for the purpose of comparison and evaluative judgment (Leech & Sharp, 2014; Morris & Mograbi, 2013). Working together, the PCC and vMPFC may mediate the retrieval, manipulation, comparison and integration of information about one's life to derive meaning and value of past and present experiences (D'Argembeau et al., 2014). Their disconnection from MT structures in the CAM would impair evaluative judgements of the present self in AD.

In neuroimaging studies, the posterior IPL is particularly active when episodic memories are successfully retrieved (Wagner, Shannon, Kahn, & Buckner, 2005). Some authors have proposed that the posterior IPL might play a role in integrating the contextual information retrieved via other MT regions (Vilberg & Rugg, 2008). Accordingly, bilateral posterior parietal lobe damage impairs the ability to fully re-experience past autobiographical events (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007). An influential model proposed that a Conscious Awareness System would be located in parietal regions (McGlynn & Schacter, 1989). However, subregions in the IPL might have different functional characteristics, and their precise role remains a matter of debate (Rugg & King, 2018). According to the CAM, conscious metacognitive awareness would emerge from the interaction between multiple modules (Figure 3).

4.3 | Limitations

A limitation in this project is that, even if results were consistent, we did not test reproducibility between our studies. The connectivity analyses were performed with different seed regions and different anosognosia scores in different samples of AD participants. Accordingly, the use of seed regions from Study 1 into Study 2 did not provide any significant results when another anosognosia score was used. Importantly, anosognosia is particularly related, but is not limited, to dysfunction of the DMN (Genon & Salmon, 2018).

5 | CONCLUSION

AD patients provided judgements on their current memory functioning that diverged from their relatives' judgements (Study 1) and from objective memory evaluation (Study 2), indicating impaired self-appraisal. Unawareness of memory impairments was related to decreased connectivity within the DMN's MT subsystem, and decreased connectivity between the MT and other DMN subsystems. Accordingly, dysfunctional networks involved in impaired episodic memory and impaired evaluative judgment both contributed to anosognosia in our patients. Moreover, impaired connectivity was observed between the MT subsystem and the middle temporal gyrus, which is probably responsible for impaired exchanges between current information and personal database for providing self-evaluation. A research perspective when including brain networks in models of anosognosia is that their effective connectivity could be further evaluated with activation fMRI paradigms, using self-related (Ruby et al., 2009) or metacognitive tasks. Another approach might be to assess brain connectivity before and after cognitive rehabilitation and/or behavioral intervention for anosognosia.

ACKNOWLEDGMENTS

We thank all members of GIGA-CRC-IVI for producing the radiotracers and for assistance with patient, behavioral and imaging data acquisition. This work was supported by grants from the Fondation Roi Baudouin (Prix Maria Elisa et Guillaume de Beys), Belgian National Funds for Scientific Research F.R.S-FNRS, Belgian Inter University Attraction Pole 7/11, University of Liège Research Concerted Action 12/17-01. The work benefited from an Investigator Sponsored Study (ISS290) from GE Healthcare for [18F]flutemetamol delivery. NA was a Candidate PhD Specialist, FC is a Research Director, CP is a Senior Research Associate, and CB is a Research Associate at FRS-FNRS, and SG is supported by the Deutsche Forschungsgemeinschaft (DFG: GE 2835/1-1). Study 1 in this work was published as a conference abstract (https://doi.org/10.1016/j.jalz.2016.06.512). Data are available on request.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ORCID

Eric Salmon https://orcid.org/0000-0003-2520-9241

REFERENCES

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, *45*, 1363–1377.

Agnew, S. K., & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: A review of the literature and a proposed model. *Aging & Mental Health*, *2*, 7–19.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron*, *65*, 550–562.

Berlingeri, M., Ravasio, A., Cranna, S., Basilico, S., Sberna, M., Bottini, G., & Paulesu, E. (2015). Unrealistic representations of "the self": A cognitive neuroscience assessment of anosognosia for memory deficit. *Consciousness and Cognition*, *37*, 160–177.

Berryhill, M. E., Phuong, L., Picasso, L., Cabeza, R., & Olson, I. R. (2007). Parietal lobe and episodic memory: Bilateral damage causes impaired free recall of autobiographical memory. *The Journal of Neuroscience*, *27*, 14415–14423.

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences*, *15*, 527–536.

Bird, C. M., Keidel, J. L., Ing, L. P., Horner, A. J., & Burgess, N. (2015). Consolidation of complex events via reinstatement in posterior cingulate cortex. *The Journal of Neuroscience*, *35*, 14426–14434.

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: A neural model of spatial memory and imagery. *Psychological Review*, *114*, 340–375.

Chavoix, C., & Insausti, R. (2017). Self-awareness and the medial temporal lobe in neurodegenerative diseases. *Neuroscience and Biobehavioral Reviews*, *78*, 1–12.

Clare, L., Markova, I., Verhey, F., & Kenny, G. (2005). Awareness in dementia: A review of assessment methods and measures. *Aging & Mental Health*, *9*, 394–413.

Clare, L., Markova, I. S., Roth, I., & Morris, R. G. (2011). Awareness in Alzheimer's disease and associated dementias: Theoretical framework and clinical implications. *Aging & Mental Health*, *15*, 936–944.

Clare, L., Whitaker, C. J., & Nelis, S. M. (2010). Appraisal of memory functioning and memory performance in healthy ageing and early-stage Alzheimer's disease. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *17*, 462–491.

Clare, L., Wilson, B. A., Carter, G., Roth, I., & Hodges, J. R. (2002). Assessing awareness in early-stage Alzheimer's disease: Development and piloting of the memory awareness rating scale. *Neuropsychological Rehabilitation*, *12*, 341–362.

D'Argembeau, A., Cassol, H., Phillips, C., Balteau, E., Salmon, E., & Van der Linden, M. (2014). Brains creating stories of selves: The neural basis of autobiographical reasoning. *Social Cognitive and Affective Neuroscience*, *9*, 646–652.

Deichmann, R., Schwarzbauer, C., & Turner, R. (2004). Optimisation of the 3D MDEFT sequence for anatomical brain imaging: Technical implications at 1.5 and 3 T. *NeuroImage*, *21*, 757–767.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Galeone, F., Pappalardo, S., Chieffi, S., Iavarone, A., & Carlomagno, S. (2011). Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *26*, 695–701.

Genon, S., & Salmon, E. (2018). Disrupted self in Alzheimer's disease: Beyond midline structures: Commentary on Wong et al. *Cortex*, *104*, 128–129.

Gerretsen, P., Chung, J. K., Shah, P., Plitman, E., Iwata, Y., Caravaggio, F., … for the Alzheimer's Disease Neuroimaging Initiative. (2017). Anosognosia is an independent predictor of conversion from mild cognitive impairment to Alzheimer's disease and is associated with reduced brain metabolism. *The Journal of Clinical Psychiatry*, *78*, e1187–e1196.

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *Journal of Neurophysiology*, *100*, 129–139.

Kurth, S., Moyse, E., Bahri, M. A., Salmon, E., & Bastin, C. (2015). Recognition of personally familiar faces and functional connectivity in Alzheimer's disease. *Cortex*, *67*, 59–73.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*, *9*, 179–186.

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, *137*, 12–32.

Martinelli, P., Anssens, A., Sperduti, M., & Piolino, P. (2013). The influence of normal aging and Alzheimer's disease in autobiographical memory highly related to the self. *Neuropsychology*, *27*, 69–78.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patients. In L. Bellack & B. Karasu (Eds.), *Geriatric psychiatry* (pp. 77–121). New York: Grune & Stratton.

McGlynn, S. M., & Schacter, D. L. (1989). Unawareness of deficits in neuropsychological syndromes. *Journal of Clinical and Experimental Neuropsychology*, *11*, 143–205.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, *7*, 263–269.

Mimura, M., & Yano, M. (2006). Memory impairment and awareness of memory deficits in early-stage Alzheimer's disease. *Reviews in the Neurosciences*, *17*, 253–266.

Morris, J. C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. *Neurology*, *43*, 2412–2414.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*, *49*, 1553–1565.

Nelissen, N., Van Laere, K., Thurfjell, L., Owenius, R., Vandenbulcke, M., Koole, M., … Vandenberghe, R. (2009). Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. *Journal of Nuclear Medicine*, *50*, 1251–1259.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain–a meta-analysis of imaging studies on the self. *NeuroImage*, *31*, 440–457.

Perrotin, A., Desgranges, B., Landeau, B., Mezenge, F., La Joie, R., Egret, S., … Chetelat, G. (2015). Anosognosia in Alzheimer disease: Disconnection between memory and self-related brain networks. *Annals of Neurology*, *78*, 477–486.

Rey, A. (1964). *L'examen clinique en psychologie*. Paris: Presse Universitaires de France.

Ries, M. L., McLaren, D. G., Bendlin, B. B., Xu, G., Rowley, H. A., Birn, R., … Johnson, S. C. (2012). Medial prefrontal functional connectivity–Relation to memory self-appraisal accuracy in older adults with and without memory disorders. *Neuropsychologia*, *50*, 603–611.

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase*, *17*, 231–241.

Rosen, H. J., Alcantar, O., Rothlind, J., Sturm, V., Kramer, J. H., Weiner, M., & Miller, B. L. (2010). Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *NeuroImage*, *49*, 3358–3364.

Ruby, P., Collette, F., D'Argembeau, A., Peters, F., Degueldre, C., Balteau, E., … Salmon, E. (2009). Perspective taking to assess self-personality: what's modified in Alzheimer's disease? *Neurobiology of Aging*, *30*, 1637–1651.

Rugg, M. D., & King, D. R. (2018). Ventral lateral parietal cortex and episodic memory retrieval. *Cortex*, *107*, 238–250.

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., … Garraux, G. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Human Brain Mapping*, *27*, 588–597.

Schachter, D. L. (1991). Unawareness of deficit and unawareness of knowledge in patients with memory disorders. In G. P. Prigatano & D. L. Schachter (Eds.), *Awareness of deficit after brain injury: Clinical and theoretical issues* (pp. 127–151). New York, NY, US: Oxford University Press.

Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H. C., Vermersch, P., … Valk, J. (1992). Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: Diagnostic value and neuropsychological correlates. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*, 967–972.

Sha, Z., Wager, T. D., Mechelli, A., & He, Y. (2019). Common dysfunction of large-scale neurocognitive networks across psychiatric disorders. *Biological Psychiatry*, *85*, 379–388.

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex*, *61*, 64–73.

Sunderaraman, P., & Cosentino, S. (2017). Integrating the constructs of Anosognosia and metacognition: A review of recent findings in dementia. *Current Neurology and Neuroscience Reports*, *17*, 27.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, *44*, 2189–2208.

Therriault, J., Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Kang, M. S., Struyfs, H., … For the Alzheimer's Disease Neuroimaging Initiative. (2018). Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology*, *90*, e932–e939.

Thurfjell, L., Lilja, J., Lundqvist, R., Buckley, C., Smith, A., Vandenberghe, R., & Sherwin, P. (2014). Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: Concordance with visual image reads. *Journal of Nuclear Medicine*, *55*, 1623–1628.

Tondelli, M., Barbarulo, A. M., Vinceti, G., Vincenzi, C., Chiari, A., Nichelli, P. F., & Zamboni, G. (2018). Neural correlates of Anosognosia in Alzheimer's disease and mild cognitive impairment: A multi-method assessment. *Frontiers in Behavioral Neuroscience*, *12*, 100.

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology*, *53*, 1–25.

Vann, S. D., Aggleton, J. P., & Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews. Neuroscience*, *10*, 792–802.

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., … Sperling, R. A. (2017). Anosognosia for memory deficits in mild cognitive impairment: Insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin*, *15*, 408–414.

Vilberg, K. L., & Rugg, M. D. (2008). Memory retrieval and the parietal cortex: A review of evidence from a dual-process perspective. *Neuropsychologia*, *46*, 1787–1799.

Vogt, B. A., Vogt, L., & Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. *NeuroImage*, *29*, 452–466.

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences*, *9*, 445–453.

Weiler, M., Northoff, G., Damasceno, B. P., & Balthazar, M. L. F. (2016). Self, cortical midline structures and the resting state: Implications for

Alzheimer's disease. *Neuroscience and Biobehavioral Reviews*, *68*, 245–255.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, *2*, 125–141.

Wilson, B. A., Cockburn, J., & Baddeley, A. D. (1985). *The Rivermead behavioural memory test*. Bury St Edmunds, UK: Thames Valley Test Company.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., … Petersen, R. C. (2004). Mild cognitive impairment–beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment. *Journal of Internal Medicine*, *256*, 240–246.

Zamboni, G., & Wilcock, G. (2011). Lack of awareness of symptoms in people with dementia: The structural and functional basis. *International Journal of Geriatric Psychiatry*, *26*, 783–792.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*, 361–370.

How to cite this article: Antoine N, Bahri MA, Bastin C, et al. Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum Brain Mapp*. 2019;1–11. https://doi.org/10.1002/hbm.24775