REVIEW ARTICLE

International Journal of Geriatric Psychiatry

Lack of awareness of symptoms in people with dementia: the structural and functional basis

G. Zamboni[1,2] and G. Wilcock[1]

[1]OPTIMA Project, Nuffield Department of Clinical Medicine, University of Oxford, UK
[2]FMRIB Centre, University of Oxford, UK
Correspondence to: G. Zamboni, E-mail: giovanna.zamboni@ndm.ox.ac.uk

Objective: To review studies investigating the brain correlates of unawareness of cognitive and behavioural symptoms in people with dementia.

Design: A detailed search of the literature was conducted to include all the peer-reviewed studies published in English aimed at identifying the structural or functional brain correspondents of unawareness in dementia patients. Their results were interpreted in relation to the methodological differences in terms of type of dementia studied, the protocol adopted to measure lack of awareness, the imaging techniques employed, the experimental designs and statistical analyses performed.

Results: Eighteen studies undertaken to explore the functional and structural correlates of unawareness of cognitive symptoms in dementia were identified. Although their results showed a disparate range of brain correlates, they were mainly localized in frontal and temporo-parietal regions.

Conclusions: Although the anatomical correlates of unawareness of disease in dementia have not yet been exhaustively explored, understanding the correlates of unawareness may also contribute to understand the brain correlates of self-awareness and self-reflection. We discuss the current knowledge base and consider potential future directions for research.

Key words: anosognosia, unawareness, loss of insight, dementia, Alzheimer's disease, imaging, functional MRI, PET, SPECT
History: Received 29 April 2010; Accepted 20 July 2010; Published online 29 October 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/gps.2620

Introduction

Patients with Alzheimer's disease and other neurodegenerative dementias are frequently unaware of their cognitive symptoms and medical diagnosis. The inability to recognize cognitive, behavioural or functional impairment occurring as a consequence of a dementing illness has been variably termed as *anosognosia*, *loss of insight*, *unawareness of illness* (Ecklund-Johnson and Torres, 2005) or *impaired self-awareness* (Prigatano, 2009). The term 'anosognosia' was initially used in clinical neurology to define unawareness of hemiplegia in patients with stroke or focal brain lesions but its use has been subsequently extended to other neurological symptoms including cognitive impairment. 'Loss of insight' and 'denial of illness' have been used with a more psychological connotation, implying a specific interpretation on the underlying mechanism. Instead, the terms 'metacognition' (Cosentino and Stern, 2005) and 'metamemory' (Pannu and Kaszniak, 2005) have been used in more operational approaches focused on specific cognitive deficits occurring in dementia (i.e. memory impairment). In this review we use 'unawareness' and its counterpart 'self-awareness' in their broadest sense to include all the different connotations and approaches implied when studying the inability to recognize symptoms in patients with neurodegenerative dementias.

The study of the neuropsychological and psychological mechanisms underlying unawareness of illness in dementia has attracted the attention of many authors. The reasons for such interest are both practical/clinical and theoretical in nature. From a practical/clinical point of view, unawareness of illness in dementia has been associated with diminished compliance with treatment, increased exposure to hazardous behaviours, and increased caregiver burden (see Aalten *et al*., 2006). In addition, unawareness of illness may challenge early diagnosis and identification of those who are at risk of developing Alzheimer's disease, given that the diagnosis of mild cognitive impairment also requires subjective memory complaint (Petersen *et al*., 1999) although this has recently become matter of discussion (Portet *et al*., 2006). From a more theoretical point of view, unawareness in dementia offers a window into the mechanisms underlying self-awareness and consciousness, as critical components of human cognition. As such, studying the neuropsychological mechanisms of unawareness of illness in patients with dementia represents a significant contribution to the field of cognitive neuroscience.

Here we review studies investigating the anatomical correlates of unawareness of cognitive deficits in Alzheimer's disease and other forms of dementia. Whereas the mechanisms of self-unawareness in terms of neuropsychological and psychological correlates have been largely reviewed, the number of studies focusing on the anatomical correlates, either structural or functional, is much smaller and has not been specifically reviewed from this perspective. However, we believe that a clearer understanding of the brain correlates of unawareness of illness in dementia (not only of the neuropsychological mechanisms) would help to better address some of the practical/clinical and theoretical issues mentioned above. At the practical/clinical level, if we consider that imaging techniques are increasingly used routinely in the diagnosis of dementia (Dubois *et al*., 2007), knowing which brain regions are involved in unawareness of disease may help to better characterize patients clinically. For example, in the early phase it could help to identify those at risk of dementia when they do not have memory complaints. Or it could help to identify patients at major risk of developing dangerous behaviour. At a more theoretical level, knowing which brain regions are involved in unawareness of symptoms in dementia could help to choose the best neuropsychological model among those proposed by alternative theories in the metacognitive and anosognosia literature (for a review see Kaszniak and Edmonds, 2010).

Here we focus on studies primarily aimed at studying the structural or functional correlates of unawareness in patients with dementia, which have measured unawareness directly and used this measurement as the grouping or dependent variable. In addition, we also review functional imaging studies that have used theoretically driven tasks designed to explicitly elicit self-awareness and its constituents (i.e. self-appraisal) in dementia patients. We include all neurodegenerative dementias. Among these, we anticipated that Alzheimer's disease would be the more extensively investigated because of its higher frequency compared to other dementias, and the high rate of unawareness of cognitive problems reported in these studies. We also expected that the second most investigated dementia would be frontotemporal dementia, in which loss of insight is one of the core diagnostic criteria (Neary *et al*., 1998).

Materials and methods

We performed searches using PubMed Services and Medline for studies including relevant keywords ('unawareness', 'anosognosia') in conjunctions with keywords related to dementia ('dementia', 'Alzheimer's disease', 'mild cognitive impairment', 'frontotemporal dementia'). We then selected only papers designed to explore the anatomical correlates of unawareness of illness by using *in vivo* imaging techniques, either structural (MRI) or functional (SPECT, PET, functional MRI), or histopathological measurements in post-mortem data. Additional publications were identified from references of the obtained articles.

Results

Eighteen studies were selected as meeting the criteria for inclusion in the review (Table 1). They were all aimed at investigating the functional or structural brain correlates of unawareness in patients with neurodegenerative dementia. They differ in terms of (i) diagnosis of the patient sample included, (ii) method of measurement of unawareness and (iii) neuroimaging technique, study design and imaging analysis adopted.

Diagnosis

Of the 18 studies, 11 were on patients with a diagnosis of Alzheimer's disease (AD), two on patients with a diagnosis of mild cognitive impairment (MCI) and two on patients with the behavioural variant of FTD. The remaining three studies looked at the correlates of

Table 1 Summary of studies of brain correlates of unawareness in dementia

Study	Participants	Unawareness measurement	Domain of unawareness	Imaging technique	Study design	Imaging analysis	Results (brain regions involved in unawareness)
Reed *et al.*, 1993	20 AD (subset of 57)	Clinical judgment	Memory	Functional: SPECT	Groups comparison: patients divided in three groups on unawareness score	Semiquantitative measurement of hypo-metabolism from ROIs	Right dorso-lateral frontal cortex
Starkstein *et al.*, 1995	24 AD (subset of 46)	Patient–informant discrepancy	Cognitive and behavioural abilities	Functional: SPECT	Groups comparison: patients divided in two groups on unawareness score	Semiquantitative measurement of rCBF from ROIs	Right inferior-orbital frontal and right frontal-superior frontal cortex
Ott *et al.*, 1996	40 (AD, depression, parkinsonian syndromes, FTD)	Clinical judgment	Global insight on cognitive and functional abilities	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Semiquantitative measurement of rCBF from ROIs	Right tempor-occipital cortex
Derouesne *et al.*, 1999	78 AD (subset of 88)	Clinical judgment and Patient–informant discrepancy	Several cognitive domains	Functional: SPECT	Groups comparison: patients divided in two groups on imaging pattern	Semiquantitative classification of scans on hypo-perfusion in selected ROIs	Right frontal lobe
Marshall *et al.*, 2004	26 AD	Clinical judgment	Global insight	Structural: histopathology	Groups comparison: patients divided in two groups on unawareness score	Plaques and neurofibrillar tangles measurement in ROIs	Right hippocampal prosubiculum
Vogel *et al.*, 2005	36 AD 30 MCI 33 controls	Patient–informant discrepancy	Memory	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Semiquantitative measurement of rCBF from ROIs	Right inferior frontal gyrus
Harwood *et al.*, 2005	41 AD	Clinical judgment	Global insight	Functional: FDG-PET	Correlation between unawareness and hypo-metabolism	Semiquantitative measurement of rCBF from ROIs	Right lateral and dorsolateral frontal cortices
Mendez and Shapira, 2005	29 FTD (frontal variant)	Clinical judgment	Global insight	Functional: SPECT or FDG-PET	Groups comparison: patients divided in four groups on imaging pattern	Qualitative classification of scans on pattern of hypo-perfusion or hypo-metabolism	Right frontal lobe
Mimura and Yano, 2006	24 AD 16 controls	Patient's judgment on self-performance	Memory	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Whole brain voxel-based analysis (SPM99)	Medial frontal lobe (Talairach coordinates: 0, 57, −16), right precuneus (8, −48, 48), right inferior frontal gyrus (38, 25, 1)
Salmon *et al.*, 2006	209 AD	Patient's judgment on self-performance and patient–informant discrepancy	Several cognitive domains	Functional: FDG-PET	Correlation between unawareness and hypo-metabolism	Whole brain voxel-based analysis (SPM99)	Self-assessment: right paraippocampus (MNI coordinates: 22, −12, −30) and left orbitofrontal cortex (−18, 36, −16) Discrepancy: left temporo-parietal junction (−56, −56, 32)
Ries *et al.*, 2007	16 MCI 16 controls	Patient–informant discrepancy (IQCODE)	Memory	Functional MRI, task related (self-personality judgment)	Groups comparison on self-awareness task + correlation between unawareness and functional activation	Voxel-based analysis in functional ROIs (SPM2)	Controls > MCI: medial frontal cortex (MNI coordinates: −4, 36, −4 and 12, 46, 16) and posterior cingulate (−6, −50, 40) correlation with unawareness in MCI patients: medial frontal cortex (6, 60, −2 and −4, 54, 14) and posterior cingulate (−6, −58, 26)
Ruby *et al.*, 2007	16 FTD 16 controls	Patient–informant discrepancy	Personality changes and social behaviour	Functional: FDG-PET	Correlation between unawareness and hypo-metabolism	Whole brain voxel-based analysis (SPM2)	Left temporal pole (MNI coordinates: −40, 12, −20)
Hanyu *et al.*, 2007	43 MCI	Patient–informant discrepancy	Memory	Functional: SPECT	Groups comparison: patients divided in two groups on imaging pattern	Qualitative classification in AD pattern and non-AD pattern of hypo-perfusion	Bilateral parietotemporal or posterior cingulated areas
Shibata *et al.*, 2008	29 AD	Patient–informant discrepancy	Memory	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Whole brain voxel-based analysis (SPM2)	Left orbitofrontal cortex (MNI coordinates: −8, 38, 0)
Hanyu *et al.*, 2008	38 AD	Patient–informant discrepancy (Wilson *et al.*, 1989)	Memory	Functional: SPECT	Groups comparison: patients divided in two groups on unawareness score	Whole brain voxel-based analysis (3D-SSP with Neurostat)	Bilateral lateral and medial frontal lobes, bilateral anterior and posterior cingulate, and left inferior parietal cortex (coordinates not reported)

(*Continues*)

Table 1. (Continued)

Study	Participants	Unawareness measurement	Domain of unawareness	Imaging technique	Study design	Imaging analysis	Results (brain regions involved in unawareness)
Ruby *et al*., 2008	14 AD 17 elderly controls 17 young controls	Patient–informant discrepancy	Personality changes	Functional MRI, task related (self/other personality judgments)	Groups comparison on self-awareness task	Whole brain voxel-based analysis (SPM2)	AD > elderly controls during self-awareness: bilateral intra-parietal sulcus (MNI coordinates: −22, −66, 40 and −26, −50, 42)
Rosen *et al*., 2010	39 (2 controls, 2 ASL, 9 AD, 2 MCI, 20 FTD, 4 CBS)	Patient's judgment on self-performance	Several cognitive domains	Structural: MRI	Correlation between unawareness and grey matter atrophy	Whole brain voxel-based analysis (SPM5)	Right orbito-medila frontal cortex (8, 18, −14)
Zamboni *et al*., 2010	64 (38 FTD and 26 CBS)	Patient–informant discrepancy	Behavioural disturbances	Structural: MRI	Correlation between unawareness and grey matter atrophy	Whole brain voxel-based analysis (SPM5)	Right temporo-parietal junction (MNI coordinates: 61, −35, 2 and 59, −24, −4) and right superior temporal sulcus (52, −37, −27)

AD, Alzheimer's disease; MCI, mild cognitive impairment; FTD, frontotemporal degeneration; CBS, corticobasal degeneration syndrome; SPECT, single photon emission computed tomography; FDG-PET, Fludeoxyglucose-photon emission tomography; MRI, magnetic resonance imaging; rCBF, regional cerebral blood flow; ROIs, region of interests; SPM, statistical parametric mapping (followed by number of program version).

unawareness combining patients with different forms of neurodegenerative dementia or pre-dementia.

Measurement of unawareness

Different methods were adopted to measure unawareness of illness in patients with dementia, and can be grouped in three main categories: (i) measurements based on the discrepancy between patients and their caregivers on a specific questionnaire assessing certain symptoms; (ii) measurements based on the patient ability to prospectively or retrospectively predict their performance on neuropsychological tests (usually adjusted for the performance itself) and (iii) measurements based on the examiner's judgment. An additional source of variability was created by the fact that unawareness can be measured in relation to different cognitive and behavioural domains (i.e. memory, behaviour, functioning on activities of daily living). Whereas measurements based on examiner's ratings usually referred to global and general unawareness (including cognitive, behavioural and functional abilities), measurements of discrepancy and performance variably referred to different specific domains depending on the questionnaire and neuropsychological tests adopted.

Imagining techniques, experimental designs and statistical analyses

All but one of the identified studies aimed to explore the relationship between brain function and unawareness used *in vivo* functional or structural imaging techniques. Only one study explored the relation between *post-mortem* histopathological changes and unawareness in AD patients, by comparing aware and un-aware patients (Marshall *et al*., 2004). Although this study is substantially different and cannot be considered a neuroimaging study, we decided to include it because its aim of identifying the pathological correlates of unawareness is similar to the aim of structural neuroimaging studies.

Among the neuroimaging studies, nine used resting SPECT (single photon emission computed tomography) as a functional technique that measures cerebral blood flow at rest. Of these, most used semiquantitative analyses to quantify the regional cerebral blood flow (rCBF) measuring the radioactive density of a certain region of interest compared to a reference region (cerebellum or occipital cortex). Four other studies used FDG-PET (fluorodeoxyglucose photon emission tomography), which measures glucose metabolism at rest. Two used functional MRI, which measures changes over time of a signal (BOLD, blood oxygen level dependent signal) indirectly reflecting neural activity that occurs when performing a cognitive task. Lastly, the two most recent studies (published in 2010) used a *structural* imaging technique (structural MRI) and were aimed at exploring the association between brain atrophy and unawareness with a voxel-based approach (see below for further explanation).

Identifying the anatomical correlates of a certain variable in diseases like dementia, in which the neurodegenerative process is widespread in the brain and involves different brain regions to a variable extent, poses more technical problems than defining focal lesions (such as stroke or brain injury). Many authors have solved this issue with a *region of interest* (ROI) approach, i.e. focusing only on brain regions (defined anatomically in variable ways) for which they had an *a priori* hypothesis and measuring the brain functional parameters only from these regions. An alternative approach which has become available more recently is to use statistical tools that allow whole brain analyses, 'dividing' the brain in units of volume (voxels) and performing statistics usually based on the general linear model to infer which variables can explain the structural/functional measurement extracted from each voxel (voxel-based approach). The great advantage of these whole-brain analyses is that they do not require *a priori* assumptions about the anatomical distribution of the structural/functional changes associated with the variable of interest.

To investigate the neuro-anatomical correlates of unawareness, authors used different experimental designs, which can be classified in three main categories. The most frequently used approach was to perform regression analyses to determine potential correlations between degree of unawareness and a numeric variable representing regional brain function (i.e. perfusion, metabolism) or structure (i.e. grey matter atrophy, amount of senile plaques). This correlational approach was used in 10 studies of those identified, which looked for correlation either in specific regions of interest or at the or whole-brain level. Another approach was to perform groups comparison, and this was done in two different ways: dividing groups on the basis of unawareness measurement (i.e. in aware and not-aware) and measuring differences on brain structure or function (Starkstein *et al*., 1995), or dividing groups on the basis of neuroimaging characteristics and measuring differences on unawareness measures (Mendez and Shapira, 2005; Hanyu *et al*., 2007). In the first case the grouping variable was the unawareness score and the dependent variable a certain imaging parameter expressing regional function, and in the second case the grouping variable was an imaging characteristic and the dependent variable the unawareness score.

Functional MRI paradigms measuring self-awareness

We mentioned that unawareness measurements were used as dependent or independent variables to study their relationship with functional or structural variables (i.e. each subject had a certain unawareness score to be associated with a certain brain parameter).

In addition, in the two studies using task related functional MRI (Ries *et al*., 2007; Ruby *et al*., 2008), brain regions involved in self-awareness could be directly explored while subjects were performing a cognitive task that involved self-awareness. These two studies adopted functional paradigms previously used in task-related functional imaging studies investigating the correlates of self-awareness in healthy subjects, with the difference that here the task was performed by patients. During the scan, patients were asked to judge themselves on several personality traits. The resulting activations were compared with activations occurring when judging the same traits in reference to others (Ruby *et al*., 2008) or when judging if the traits were positive or negative (Ries *et al*., 2007).

Neuro-anatomical correspondents of unawareness

We will discuss the main results of the reviewed papers in terms of brain localization, with respect of whether the main results included frontal regions, temporo-parietal regions, or both frontal and temporo-parietal regions.

Frontal regions. The first studies conducted under the hypothesis that unawareness of memory problems is associated with regional cerebral function in AD adopted a group-comparison approach (Reed *et al*., 1993; Starkstein *et al*., 1995). In these studies, AD patients were divided into groups according their degree of unawareness and the SPECT regional cerebral blood flow (rCBF) of different regions of interest (including parietal, frontal and temporal ROIs) was compared between groups. In both the studies the results showed that patients with greater degree of unawareness had significantly lower rCBF in right-sided frontal regions compared to patients more aware of their memory problems. However, the frontal ROIs were variably anatomically defined and, whereas Reed and colleagues only found significant differences between groups in the right dorso-lateral frontal ROI (Reed *et al*., 1993), Starkstein and colleagues, who also matched patients on neuropsychological performance found additional differences in the infero-orbital frontal ROI (Starkstein *et al*., 1995). Similarly, a significant association between frontal, right-sided hypo-perfusion and unawareness of cognitive deficits were found in another SPECT study, in which AD patients were divided into groups on the basis of pattern of cerebral hypo-perfusion (frontal, parieto-temporal and frontotemporoparietal) and the unawareness score was measured as the dependent variable. In this study, the unawareness score was significantly higher in patients with a predominant frontal or frontotemporoparietal perfusion deficit than in patients with a pure parietotemporal deficit and tended to be higher in patients with a predominant right hemisphere deficit (Derouesne *et al*., 1999). Analogous results were obtained in another study conducted on patients with FTD, divided into groups on the basis of predominant frontal or temporal hypoperfusion or hypometabolism (Mendez and Shapira, 2005).

Other authors explored further the association between unawareness of memory impairment in patients with AD/MCI and the frontal lobes using a correlational approach (Harwood *et al*., 2005; Vogel *et al*., 2005). In a SPECT analysis, Vogel and colleagues found a significant correlation between unawareness and the rCBF of the right inferior frontal gyrus (situated in the inferior lateral part of the frontal lobe) but not middle frontal gyrus (dorsolateral frontal cortex) or orbitofrontal cortex (Vogel *et al*., 2005). In a PET experiment, Harwood and colleagues studied the glucose metabolism of 13 regions in which they had divided the frontal lobes (Harwood *et al*., 2005) and found that poorer awareness of cognitive impairment correlated with the rate of hypometabolism in the right lateral and dorsolateral frontal cortices. This association was not influenced by other factors such as age and global cognitive impairment. All these studies had examined only a limited number of brain regions focusing on ROIs and some (Harwood *et al*., 2005; Vogel *et al*., 2005) specifically only on ROIs in the frontal lobes, therefore the interpretation of their results is limited *a priori* by the criteria they used to choose and anatomically define their ROIs.

After whole-brain voxel-based approaches became available, only a few studies showed unique involvement of frontal regions. Among these, Shibata *et al*. (2008), by using a correlational analysis on whole-brain SPECT data, identified a small region in the left orbitofrontal cortex where perfusion correlated with unawareness of memory impairment (results were not corrected for multiple comparisons). With a correlational analysis performed on structural MRI data, Rosen and co-authors showed recently that unawareness measured as self-appraisal accuracy on cognitive tasks inversely correlated (at a statistical threshold corrected for multiple comparisons) with the degree of regional grey matter atrophy in the right medial orbitofrontal cortex, meaning that the larger volume of this region is associated with more accurate self-appraisal on cognitive performance (Rosen *et al*., 2010). This study was performed in a heterogeneous group, which included patients with AD, FTD and healthy controls. The authors concluded that the established role of orbitofrontal regions in emotional and physiological self-monitoring is probably also important in mediating self-awareness in dementia.

Frontal and temporo-parietal regions. Other correlational studies performed at the whole-brain level have shown the involvement of frontal regions in association with more posterior regions including medial parietal (precuneus and posterior cingulate), lateral parietal or temporal areas.

For example, Mimura *et al*. (2006) correlated SPECT perfusion with AD patients' judgment on their own performance on memory testing and found significant correlation in orbitofrontal regions and in the precuneus. Similarly, but with a functional MRI study involving self-judgment on personality traits, Ries and colleagues demonstrated that the functional activity in medial frontal cortex and posterior cingulate correlated negatively with a measure of unawareness of cognitive impairment in patient with MCI (Ries *et al*., 2007). This study suggested that unawareness of cognitive impairment may be a consequence of dysfunction of frontal and parietal regions that are involved in self-appraisal and that are vulnerable to changes associated with early AD. The same medial frontal and parietal regions were also found in a study comparing aware and less aware AD patients on pattern of SPECT hypoperfusion (Hanyu *et al*., 2008).

In a multicentre study involving several PET centres in Europe (Salmon *et al*., 2006) voxel-based correlational analyses were used to study the relationship between brain glucose metabolism in AD patients and unawareness of cognitive impairment measured in two ways: patient self-assessment and discrepancy between patient-carer. The authors found that unawareness measured by patients' self-assessment was related to dysfunction in left orbitofrontal and right parahippocampal regions, whereas unawareness measured by discrepancy between patient-carer correlated with hypometabolism in more posterior regions, including left temporo-parietal junction and inferior temporal gyrus. Interestingly, this is the only study that looked at the correlation with unawareness measured in two ways; the results support the hypothesis that different measurements of awareness may show different underlying cognitive processes and consequently have different brain correlates (see Figure 1 for a visualization of resulting regions classified according to different unawareness measurements of studies adopting a voxel-based approach).

Temporo-parietal regions. The only study that investigated the clinicopathological correlates of unawareness (Marshall *et al*., 2004) examined senile plaque and neurofibrillary tangle counts from four frontal and temporal lobe regions in both the hemispheres and compared aware and not aware AD patients groups matched on dementia severity. The authors found that senile plaque density in the prosubiculum of the hippocampus was greater in patients unaware compared to patients more aware of their cognitive impairment, with no significant differences in the other regions. However, the study had the limitation that unawareness was measured years before the patients' death and clinicopathological examination, therefore other overlapping factors may have been responsible for the differences.

Among the SPECT studies performing correlations between rCBF in specific ROIs and a measure of unawareness (i.e. Harwood *et al*., 2005; Vogel *et al*., 2005), the only one which included ROIs from all association cortices and not only from frontal lobes showed that a measure of insight based on examiner's ratings was significantly correlated with right temporo-occipital perfusion (Ott *et al*., 1996), contrasting with the hypothesis of an essential role of frontal lobes in self-awareness.

Ruby *et al.* explored the brain correlates of self-awareness in patients with a diagnosis of behavioural variant of FTD measuring the discrepancy between patient and caregiver in two questionnaires assessing personality and social behaviour in a FDG-PET study (Ruby *et al*., 2007). They performed a correlational analysis in the whole-brain (with a voxel-based approach) and found that the score measuring unawareness of social behaviour was inversely correlated with glucose metabolism in the left temporal pole, and—at a lower statistical threshold—also in the right temporal pole. In other words, the less aware of their social behaviour the patients were, the lower the glucose metabolism in the temporal poles. This suggests—according to the authors—that unawareness for social disability in FTD patients originates in impaired processing of autobiographical information

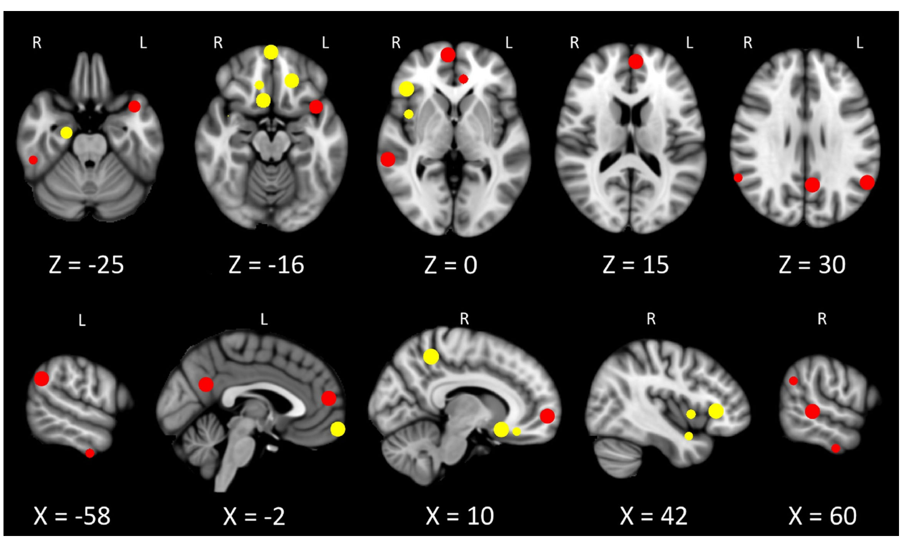

Figure 1 Brain correlates of unawareness for illness in dementia patients. The red and yellow spherical markers were centred on the regions resulting from the reviewed studies that adopted voxel-based statistical analyses (see Table 1 for a list of the specific regions and brain coordinates in each study) and displayed on the Montreal Neurological Institute (MNI) standard template. Note the involvement of frontal and parieto-temporal regions and how this affects structures of the cortical midline. Results of studies measuring unawareness as discrepancy between patient and informant are marked in red. Results of studies measuring unawareness as the patient's judgment on self-performance are marked in yellow. Large spherical markers represent results significant at $p < 0.05$ after correction for multiple comparisons, smaller markers represent results significant at $p < 0.001$, uncorrected. Coordinates are in the MNI space. L, left; R, right. This figure is available in colour online at wileyonlinelibrary.com/journal/gps

(stored in the temporal lobes) leading to a self-representation that does not match current behaviour. In a more recent functional MRI experiment, the same authors studied patients with AD and healthy controls during a task in which they had to judge themselves and a relative on several personality traits, taking either their own or their relative's perspective (Ruby *et al*., 2008). Although they did not find significant differences between patients and controls in the personality self-awareness score (assessed as discrepancy between self and relative's report), during self-assessment (in both their or their relative's perspective) healthy controls had more activation in the dorsomedial prefrontal cortex than AD patients, whereas AD patients had more activation in the intraparietal sulcus than controls. The authors speculated that AD patients rely more on semantic than episodic personal information, and more on familiarity rather than recollection when providing judgment on personality traits.

Another correlational study performed on patients with a diagnosis of the FTD spectrum (including corticobasal degeneration) using structural MRI (Zamboni *et al*., 2010) showed that increasing unawareness of behavioural impairment was associated with increasing grey matter atrophy of a more posterior temporal region (superior temporal sulcus, extending posteriory to the temporo-parietal junction) of the right hemisphere. Since these regions have a role on cognitive tasks requiring the ability of empathize with others' feelings as demonstrated by the theory-of-mind literature, the authors concluded that unawareness of behavioural impairment in patients with FTD may derive from the inability to understand others' reaction to their inappropriate behaviour.

Discussion

Unawareness of illness in neurodegenerative dementias has been studied mainly from a neuropsychological point of view. However, if unawareness in dementia is the result of damage by the neurodegenerative disease, identifying the specific brain structures involved is important to understand the underlying mechanisms of unawareness. A range of different methodological issues, including unawareness measurements, neuroimaging techniques and statistical analyses were evident within the relatively small number of studies that have explored the brain correlates of unawareness in dementia. Some studies focused on a specific cognitive domain, such as—for example—unawareness of memory deficit, whereas other considered awareness in a broader context, including impaired awareness of cognitive, behavioural and functional deficits. Most studies included only patients with a diagnosis of AD, whereas others included several neurodegenerative dementias. While individual studies may have drawn different conclusions about the brain correlates of unawareness of disease in dementia, reviewing the studies within a unique framework in which differences in aims and methods were carefully considered, allowed clarification of what is currently known about the brain correlates of unawareness in dementia and consideration of implications for future studies.

The majority of studies showed the involvement of the right hemisphere, whose specific role in unawareness has also been demonstrated in studies investigating the brain correlates of unawareness in other neuropsychiatric and neurological disorders, including traumatic brain injury, stroke and schizophrenia (Orfei *et al*., 2008). In addition, a few studies showed the involvement of cerebral medial regions (frontal or parietal or both), which, depending on the spatial resolution of the imaging technique, can easily include both left and right interfaces and do not allow a specific anatomical distinction in terms of lateralization.

Regarding the intra-hemispheric localization, the involvement of frontal and/or temporo-parietal cerebral areas was reported in all the studies. In this review single studies were presented according whether the identified anatomical correspondents of unawareness were purely frontal, both frontal and temporo-parietal, or purely temporo-parietal. Despite the extended variability in methods, this made it possible to identify common features in studies showing relatively close results in terms of anatomical localization.

Most of the earlier studies showing only frontal involvement had actually adopted regions of interest approaches and only focused on frontal regions, limiting the possible interpretation. However, two studies demonstrated a unique frontal involvement using a whole brain approach (Shibata *et al*., 2008; Rosen *et al*., 2010), both showing a medial-orbital involvement of the frontal lobes rather than dorsolateral. Among the other seven studies adopting a whole-brain voxel-based approach, three showed the common involvement of medial frontal and parietal regions (Mimura and Yano, 2006; Ries *et al*., 2007; Hanyu *et al*., 2008).

When unawareness was measured using patients' retrospective judgment of their own performance on neuropsychological tests, a frontal involvement was demonstrated (Mimura and Yano, 2006; Salmon *et al*., 2006; Rosen *et al*., 2010). Instead, when measured from patient–carer discrepancy, different regions emerged. As for the cognitive domain, when unawareness was measured with respect to the personality or behavioural changes occurring with the disease, the unique involvement of lateral temporal-parietal regions emerged (Ruby *et al*., 2007; Ruby *et al*., 2008; Zamboni *et al*., 2010). To disentangle the effect of these methodological factors, future studies should include different unawareness measurements (self-assessment, discrepancy, examiner's judgment) and domain (cognitive, behavioural, functional) in the same study and imaging analysis, to explore the correlates of each aspect controlling for the others.

In conclusion, critical areas including medial frontal, medial parietal and lateral parieto-temporal regions emerged in this review. Some of these areas have been frequently associated with poor awareness also in other neurological disorders. This suggests that these regions may be part of an 'awareness system' that—if damaged—leads to different types of unawareness (Prigatano, 2009). Several task-related functional imaging studies have shown that the same regions are involved in appraisal of self-relevant information in healthy subjects (Northoff and Bermpohl, 2004; Amodio and Frith, 2006). More precisely the involvement of cortical midline structures, including medial prefrontal cortex and medial posterior cingulate/precuneus has been shown in studies requiring self-referential compared to other-referential judgments or thoughts. Another line of functional MRI studies has shown the involvement of medial frontal and lateral parieto-temporal regions (including the temporo-parietal junction) in the ability to interpret other's mental status, also known as theory of mind or mentalizing (Decety and Sommerville, 2003; Frith and Frith, 2003). Therefore, it appears that brain regions involved in unawareness of illness in dementia are also involved in self and other processing (Johnson *et al*., 2002; Amodio and Frith, 2006).

In addition, an increasing number of functional neuroimaging studies have started to focus on spontaneous brain activity at rest. Among the several functional anatomical networks identified, one has been interpreted as the 'default-mode' network, being deactivated during performance of many cognitive tasks and 'activated' only when subjects are not engaged in external tasks. This network includes medial prefrontal, medial parietal (posterior cingulate and precuneus), lateral parietal regions, and the hippocampus, partially resembling the regions emerged in the present review as well as the regions involved in self-appraisal in task-related functional MRI. Among several explanations suggested for the default mode network, the fact that it may reflect self-reflection processes has been argued by many authors. In addition, it has been shown that the default mode network activity is reduced in AD. If unawareness is the consequence of impaired self-reflection mechanisms and the brain correlates of self-reflection correspond to the default-mode network, one would expect that the reduced default mode activity seen in AD indeed reflects their impaired awareness. Future studies should directly explore the correlation between unawareness, the default-mode network and regions engaged in self-reflection tasks.

Key Points

- Unawareness of symptoms is a common feature of dementia. It is also termed as *anosognosia*, *loss of insight*, or *impaired self-awareness*.
- The 18 studies aimed at studying whether unawareness in dementia is associated with the involvement of specific brain regions differ in terms of diagnosis of the patients included, method of measurement of unawareness, and neuroimaging technique and analysis adopted.
- The involvement of frontal, medial parietal, and lateral parieto-temporal regions emerged in this review (Figure 1).
- Those regions are known to have a role in cognitive processing of self- and other-relevant information and are part of the 'default-mode' network.

Conflict of interest

None declared.

Acknowledgements

The authors are supported by the Oxford NIHR Biomedical Research Centre. They thank Erin Drazich and Chris Daniels for paper editing.

References

Aalten P, van Valen E, de Vugt ME, *et al*. 2006. Awareness and behavioral problems in dementia patients: a prospective study. *Int Psychogeriatr* **18**: 3–17.
Amodio DM, Frith CD. 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci* **7**: 268–277.
Cosentino S, Stern Y. 2005. Metacognitive theory and assessment in dementia: do we recognize our areas of weakness? *J Int Neuropsychol Soc* **11**: 910–919.
Decety J, Sommerville JA. 2003. Shared representations between self and other: a social cognitive neuroscience view. *Trends Cogn Sci* **7**: 527–533.

Derouesne C, Thibault S, Lagha-Pierucci S, *et al*. 1999. Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. *Int J Geriatr Psychiatry* **14**: 1019–1030.
Dubois B, Feldman HH, Jacova C, *et al*. 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* **6**: 734–746.
Ecklund-Johnson E, Torres I. 2005. Unawareness of deficits in Alzheimer's disease and other dementias: operational definitions and empirical findings. *Neuropsychol Rev* **15**: 147–166.
Frith U, Frith CD. 2003. Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci* **358**: 459–473.
Hanyu H, Sakurai H, Hirao K, Shimizu S, Iwamoto T. 2007. Unawareness of memory deficits depending on cerebral perfusion pattern in mild cognitive impairment. *J Am Geriatr Soc* **55**: 470–471.
Hanyu H, Sato T, Akai T, *et al*. 2008. Neuroanatomical correlates of unawareness of memory deficits in early Alzheimer's disease. *Dement Geriatr Cogn Disord* **25**: 347–353.
Harwood DG, Sultzer DL, Feil D, *et al*. 2005. Frontal lobe hypometabolism and impaired insight in Alzheimer disease. *Am J Geriatr Psychiatry* **13**: 934–941.
Johnson SC, Baxter LC, Wilder LS, *et al*. 2002. Neural correlates of self-reflection. *Brain* **125**: 1808–1814.
Kaszniak AW, Edmonds EC. 2010. Anosognosia and Alzheimer's disease: behavioral studies. In *The Study of Anosognosia*, Prigatano G (ed.). Oxford University Press: New York.
Marshall GA, Kaufer DI, Lopez OL, *et al*. 2004. Right prosubiculum amyloid plaque density correlates with anosognosia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **75**: 1396–1400.
Mendez MF, Shapira JS. 2005. Loss of insight and functional neuroimaging in frontotemporal dementia. *J Neuropsychiatry Clin Neurosci* **17**: 413–416.
Mimura M, Yano M. 2006. Memory impairment and awareness of memory deficits in early-stage Alzheimer's disease. *Rev Neurosci* **17**: 253–266.
Neary D, Snowden JS, Gustafson L, *et al*. 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**: 1546–1554.
Northoff G, Bermpohl F. 2004. Cortical midline structures and the self. *Trends Cogn Sci* **8**: 102–107.
Orfei MD, Robinson RG, Bria P, Caltagirone C, Spalletta G. 2008. Unawareness of illness in neuropsychiatric disorders: phenomenological certainty versus etiopathogenic vagueness. *Neuroscientist* **14**: 203–222.
Ott BR, Noto RB, Fogel BS. 1996. Apathy and loss of insight in Alzheimer's disease: a SPECT imaging study. *J Neuropsychiatry Clin Neurosci* **8**: 41–46.
Pannu JK, Kaszniak AW. 2005. Metamemory experiments in neurological populations: a review. *Neuropsychol Rev* **15**: 105–130.
Petersen RC, Smith GE, Waring SC, *et al*. 1999. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**: 303–308.
Portet F, Ousset PJ, Visser PJ, *et al*. 2006. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *J Neurol Neurosurg Psychiatry* **77**: 714–718.
Prigatano GP. 2009. Anosognosia: clinical and ethical considerations. *Curr Opin Neurol.* **22**(6): 606–611.
Reed BR, Jagust WJ, Coulter L. 1993. Anosognosia in Alzheimer's disease: relationships to depression, cognitive function, and cerebral perfusion. *J Clin Exp Neuropsychol* **15**: 231–244.
Ries ML, Jabbar BM, Schmitz TW, *et al*. 2007. Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. *J Int Neuropsychol Soc* **13**: 450–461.
Rosen HJ, Alcantar O, Rothlind J, *et al*. 2010. Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *Neuroimage* **49**: 3358–3364.
Ruby P, Collette F, D'Argembeau A, *et al*. 2008. Perspective taking to assess self-personality: what's modified in Alzheimer's disease? *Neurobiol Aging.* **30**(10): 1637–1651.
Ruby P, Schmidt C, Hogge M, *et al*. 2007. Social mind representation: where does it fail in frontotemporal dementia? *J Cogn Neurosci* **19**: 671–683.
Salmon E, Perani D, Herholz K, *et al*. 2006. Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp* **27**: 588–597.
Shibata K, Narumoto J, Kitabayashi Y, Ushijima Y, Fukui K. 2008. Correlation between anosognosia and regional cerebral blood flow in Alzheimer's disease. *Neurosci Lett* **435**: 7–10.
Starkstein SE, Vazquez S, Migliorelli R, *et al*. 1995. A single-photon emission computed tomographic study of anosognosia in Alzheimer's disease. *Arch Neurol* **52**: 415–420.
Vogel A, Hasselbalch SG, Gade A, Ziebell M, Waldemar G. 2005. Cognitive and functional neuroimaging correlate for anosognosia in mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry* **20**: 238–246.
Zamboni G, Grafman J, Krueger F, Knutson KM, Huey ED. 2010. Anosognosia for behavioral disturbances in frontotemporal dementia and corticobasal syndrome: a voxel-based morphometry study. *Dement Geriatr Cogn Disord* **29**: 88–96.

