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Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex

Martina Amanzio,[1,2] Diana M. E. Torta,[1] Katiuscia Sacco,[1,2,3] Franco Cauda,[1,2,3] Federico D'Agata,[1,2,3] Sergio Duca,[2,3] Daniela Leotta,[4] Sara Palermo[1,4] and Giuliano C. Geminiani[1,2,3]

1 Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy
2 Neuroscience Institute of Turin, NIT, University of Turin, Italy
3 CCS functional MRI, Koelliker Hospital, Corso G. Ferraris 251, 10134 Turin, Italy
4 Martini Hospital, Neurology Unit, Via Tofane 71, 10100 Turin, Italy

Correspondence to: Martina Amanzio,
Department of Psychology,
University of Turin,
Via Verdi 10, 10123 Turin,
Italy
E-mail: martina.amanzio@unito.it

Unawareness of deficits is a symptom of Alzheimer's disease that can be observed even in the early stages of the disease. The frontal hypoperfusion associated with reduced awareness of deficits has led to suggestions of the existence of a hypofunctioning prefrontal pathway involving the right dorsolateral prefrontal cortex, inferior parietal lobe, anterior cingulate gyri and limbic structures. Since this network plays an important role in response inhibition competence and patients with Alzheimer's disease who are unaware of their deficits exhibit impaired performance in response inhibition tasks, we predicted a relationship between unawareness of deficits and cingulate hypofunctionality. We tested this hypothesis in a sample of 29 patients with Alzheimer's disease (15 aware and 14 unaware of their disturbances), rating unawareness according to the Awareness of Deficit Questionnaire-Dementia scale. The cognitive domain was investigated by means of a wide battery including tests on executive functioning, memory and language. Neuropsychiatric aspects were investigated using batteries on behavioural mood changes, such as apathy and disinhibition. Cingulate functionality was assessed with functional magnetic resonance imaging, while patients performed a go/no-go task. In accordance with our hypotheses, unaware patients showed reduced task-sensitive activity in the right anterior cingulate area (Brodmann area 24) and in the rostral prefrontal cortex (Brodmann area 10). Unaware patients also showed reduced activity in the right post-central gyrus (Brodmann area 2), in the associative cortical areas such as the right parietotemporal–occipital junction (Brodmann area 39) and the left temporal gyrus (Brodmann areas 21 and 38), in the striatum and in the cerebellum. These findings suggest that the unawareness of deficits in early Alzheimer's disease is associated with reduced functional recruitment of the cingulofrontal and parietotemporal regions. Furthermore, in line with previous findings, we also found apathy and disinhibition to be prominent features of the first behavioural changes in unaware patients.

Introduction

The unawareness of deficits in patients with probable Alzheimer's disease is a complex and non-unitary phenomenon (Vasterling *et al.*, 1995; Starkstein *et al.*, 1996), which has been analysed without reaching any definitive results, particularly regarding its relationship with executive dysfunctions (Agnew and Morris, 1998; Clare, 2004*a, b*; Amanzio and Torta, 2009). A variety of terms have been used to describe reduced awareness in these patients: 'lack of insight', 'anosognosia' and 'reduced awareness of deficits'. For example, 'lack of insight' usually describes the lack of introspective knowledge and metacognitive functioning in psychiatric illness; the term 'anosognosia' is typically used to describe a failure to acknowledge a particular neuropsychological deficit concerning specific modular functions (perception, action or language: anosognosia for hemiplegia, for unilateral neglect or for fluent aphasia). In this study, we chose to use the term 'reduced awareness of deficits', which is descriptive and has no theoretical implications.

Patients with early Alzheimer's disease can show impairments in the executive system (Sebastian *et al.*, 2006). This system is involved in controlling action in situations where the routine control of behaviour does not suffice, such as in situations that require the suppression of habitual or dominant responses or novel situations. Accordingly, impairments at the level of the supervisory attentional system (Norman and Shallice, 1980) are typically most apparent in daily life, where unstructured and novel situations put high demands on cognitive capacities (Krabbendam *et al.*, 1999). These deficits are often described as a dysexecutive syndrome (Baddeley, 1986). Interestingly, it has been proposed that the central executive system (Baddeley, 1986), a concept close to the supervisory attentional system, accounts for lack of awareness in patients with Alzheimer's disease (Lopez *et al.*, 1994). In particular, Lopez *et al.* (1994) suggested that unawareness in Alzheimer's disease may result from a greater impairment of the central executive system, which is a metacognitive structure involved in the control of information flow in tasks requiring initiation, planning, mental set-shifting, strategy allocation, monitoring and inhibition. A neurocognitive model of awareness in patients with Alzheimer's disease, the conscious awareness model, may help understand the link between the contribution of the executive system in metacognitive abilities related to awareness (Litvan *et al.*, 1996, 1997, 2003; Agnew and Morris, 1998; Ryan *et al.*, 2006). This model includes a comparator system within the central executive to monitor mismatches between a personal database and experienced cognitive failures and successes. When a mismatch is detected, a signal is sent to the metacognitive awareness system that leads to the conscious experience of failure. If the executive system is not functioning correctly, as observed in patients with early Alzheimer's disease (Baddeley *et al.*, 2001), the comparator mechanism does not detect mismatches. Consequently, a failure in cognitive performance may not reach metacognitive output or conscious awareness, leading to an 'executive unawareness' in the conscious awareness model. The relationship between unawareness of deficits and dysexecutive dysfunctions in patients with Alzheimer's disease has been demonstrated by many studies through neuropsychological

batteries purported to prefrontal cortex (Loebel *et al.*, 1990; Mangone *et al.*, 1991; Auchus *et al.*, 1994; Lopez *et al.*, 1994; Michon *et al.*, 1994; Ott *et al.*, 1996), and the study of cerebral perfusion using PET and single photon emission computed tomography techniques (Clare, 2004*a*). In this executive unawareness a faulty appreciation of performance, with no recognition of failure, leads to a lack of update of the patient's personal database (Mograbi *et al.*, 2009).

Since these comparator mechanisms are responsible for the monitoring of performance on different cognitive tasks, we believe that monitoring the information flow on tasks requiring inhibition of responses provides a fruitful approach to study the unawareness of deficits in patients with early Alzheimer's disease. Interestingly, subjects with Alzheimer's disease have been found to be impaired on response inhibition tasks involving divided attention abilities (Baddeley *et al.*, 2001). A relationship between response inhibition disabilities and unawareness of deficits in patients with Alzheimer's disease has been demonstrated using a neuropsychological approach (Kashiwa *et al.*, 2005). In this study, part III of the Stroop Test showed an association with unawareness. Poor performance in this part of the task is considered to reflect response inhibition deficits; studies in normal subjects have in fact demonstrated a relationship between the Stroop Test and the activity of the orbitofrontal gyrus (Goldstein *et al.*, 2001). In particular, the anterior cingulate cortex, a region of the medial-frontal circuit, has been found to be active in go/no-go tasks (low-frequency events) in normal subjects (Casey *et al.*, 1997; Braver *et al.*, 2001). This structure proved important in monitoring performance in cognitive tasks and in several aspects of affective behaviour (see the review of Devinsky *et al.,* 1995). The cognitive component of the anterior cingulate cortex has been studied in several neuroimaging studies (Carter *et al.*, 1998; Botvinick *et al.*, 1999; Barch *et al.*, 2001) focusing on the role of this area in executive functions. In particular, it has been demonstrated that the anterior cingulate cortex is active during the execution of tasks in which a prepotent response has to be overcome, such as in go/no-go tasks. However, although the association between unawareness of deficits and the cerebral regions responsible for response inhibition competences would appear to be suggestive, no studies have approached the relationship between response inhibition disabilities and unawareness of deficits in patients with Alzheimer's disease using a specific executive task (anterior cingulate cortex sensitive) during a functional MRI session. Crucially, previous studies have only analysed the differences between aware and unaware patients at an anatomical–functional level using PET and single photon emission computed tomography neuroimaging techniques in resting state conditions. In these studies, the presence of reduced awareness of deficits in patients with Alzheimer's disease was associated with decreased perfusion in the lateral right-side frontal inferior (orbital), superior (dorsolateral) (Starkstein *et al.*, 1995) and parietal region (Leys *et al.*, 1989). A more recent PET study (Salmon *et al.*, 2005) described reduced awareness of cognitive deficits in Alzheimer's disease in terms of impaired metabolism in parts of networks subserving the superior frontal sulcus and the temporo-parietal junction. Moreover, Vogel *et al.* (2005) suggested that the right inferior frontal gyrus might be a crucial area for impaired awareness. This region also has a

fundamental role in response-inhibition competence (Aron *et al.*, 2003, 2004). Finally, the neuroanatomical correlates of unawareness of memory deficits were investigated in a recent study using single photon emission computed tomography regional perfusion data (Hanyu *et al.*, 2008). The authors discovered that functional damage to the inferior, medial and orbital frontal lobes, as well as the anterior cingulate gyri, may be associated with lack of awareness in patients with early Alzheimer's disease.

Besides being involved in response inhibition tasks, the anterior cingulate cortex is also implicated in apathy (Migneco *et al.*, 2001; Levy and Dubois, 2006; Marshall *et al.*, 2007), and apathetic behaviour has been found to be associated with the unawareness of Alzheimer's disease (Starkstein *et al.*, 1996, 2006, 2007). The lack of initiative in patients with Alzheimer's disease has been negatively correlated with perfusion in the right anterior cortex (Benoit *et al.*, 2004) and apathetic subjects with Alzheimer's disease have significantly decreased perfusion of the anterior cingulate cortex bilaterally (Migneco *et al.*, 2001). This would suggest a close relationship between apathy and the unawareness phenomenon.

Thus, to better analyse unawareness in early patients with Alzheimer's disease, we conducted a convergent analysis of cognitive, anatomical–functional and behavioural levels. In particular, this deficit might be owing to dysfunction within cingulofrontal pathways implicated in response conflict monitoring. Interestingly, Starkstein *et al.* (2007) suggested that subjects with Alzheimer's disease with a more pronounced frontal hypoperfusion may develop unawareness of their deficits even at an early stage of the disease. Therefore, we predicted unaware patients to show reduced activation in the medial prefrontal circuit (and in particular, in the anterior cingulate cortex subregions), during a response inhibition (go/no-go) task compared to subjects aware of their deficits. Finally, at behavioural level, we hypothesized a more pronounced apathetic symptomatology among unaware patients.

Materials and methods

Participants

Twenty-nine right-handed consecutive outpatients were included in the study. The patients had been referred to the Unit for Alzheimer's disease evaluation of the Martini Hospital in Turin. They met the criteria of National Institute of Neurological and Communicable Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable Alzheimer's disease (McKhann *et al.*, 1984), having a Hachinski ischaemic score of ≤4; a mini-mental state examination (MMSE) score (Folstein *et al.*, 1975) of 19–24; no traumatic brain injury with loss of consciousness; no history of stroke or any other neurological or psychiatric illness; normal blood tests; no lesions detectable on MRI (T$_1$-weighted), especially in frontal areas and in the anterior cingulate cortex as assessed by a neuroradiologist (S.D.). Patients were excluded from the study if they: (i) had major depression or dysthymia, based on Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria (American Psychiatric Association, 2000); (ii) had subclinical depressive symptomatology assessed by means of a psychological evaluation; (iii) were on medication that could directly affect cognitive functioning, such as neuroleptics; or (iv) had taken antidepressants and/or anxiolytics

and/or anti-cholinesterase drugs <15 days before the neuropsychological evaluation. Handedness was rated using the Edinburg Handedness Inventory (Oldfield, 1971).

A second group of 29 normal elderly participants (the caregivers) also took part in the study in order to provide information about patients' awareness of disease with the awareness of deficit questionnaire - dementia (AQ-D) scale (Migliorelli *et al.*, 1995). Since this method is based on a subtractive index of perception by caregivers and patients, excluding any bias in caregivers' judgements is crucial. The caregivers had normal neurological and psychiatric evaluations and a negative history of neurological disorders. They were not on any medication known to affect the CNS. Mental deterioration was excluded by means of a clinical examination and MMSE. Subclinical depressive symptomatology was also excluded by means of a psychological evaluation, as it could not be assessed using psychiatric scales alone. Neuropsychiatric scales [the Hamilton depression scale (HAM-D) and the Hamilton anxiety scale (HAM-A)] and theory of mind tasks were administered to exclude any tendency towards anxiety or depressive mood and difficulty in the ability to make inferences about another individual's mental state.

The patients and caregivers participated voluntarily and all gave their informed consent prior to being recruited in the study. The study was approved by the ethical committee of the Department of Psychology, University of Turin.

Design and procedures

All behavioural test batteries and psychiatric scales were administered by a neuropsychologist blind to the aims of the study. The participants with Alzheimer's disease were assessed in three experimental sessions each lasting 1 h, on three different days 1 week apart. During the first session, the patients with Alzheimer's disease were primarily assessed on deficit awareness using the AQ-D scale and subsequently on behavioural status using the neuropsychiatric batteries. On the other 2 days they were studied using neuropsychological batteries. The caregivers were assessed during a single experimental session lasting ~1 h in the absence of the patients.

During the initial diagnostic assessment at the first examination, the neurologist (D.L.) also collected data concerning patients' awareness of deficits using the clinical insight rating scale (Ott and Fogel, 1992; Ott *et al.*, 1996), without knowing the results of the AQ-D scores.

Assessment of impaired awareness

Unawareness of deficits in the Alzheimer's disease population at the time of testing was analysed by means of a domain-specific assessment as proposed by Barrett *et al.* (2005) using the AQ-D scale (Migliorelli *et al.*, 1995). The AQ-D was used with the aim of differentiating aware and unaware patients. This is an instrument of proven reliability and validity for rating the severity of unawareness of deficits in people with Alzheimer's disease (Migliorelli *et al.*, 1995). The questionnaire consists of 30 questions divided into two sections: the cognitive and the behavioural. The cognitive part assesses cognitive function and performance, in basic and instrumental activities of daily living. The behavioural part assesses changes in interests and mood. The same questions were put to the patients (Form A) and to their caregivers (Form B) who were blind to the patients' responses. Each question has a score ranging from 0 (never) to 3 (always); the minimum and maximum total scores obtainable on each form range from 0 to 90. For the cognitive section, scores can range from 0 to 66. For the behavioural section scores can range from 0 to 24. The total AQ-D score is given by the difference between Form B and A. Higher

scores indicate a reduced awareness of deficits, meaning that care-givers rated the patients as more impaired than did the patients. Patients with a score of >32 are classified as being unaware, whereas patients with a score of <14 are classified as being aware of their deficits (Migliorelli *et al.*, 1995).

To verify the reliability of the deficit unawareness assessment, the clinical insight rating scale (Ott and Fogel, 1992; Ott *et al.*, 1996) was used and its score was correlated to the AQ-D score. The clinical insight rating scale evaluates the reason for the examination, cognitive deficits, functional deficits and the perception of the progression of the disease. Each item has a score ranging from 0 to 2, with a total score between 0 (insight preserved) and 8 (absence of insight). Ratings on the clinical insight rating scale were carried out by a neurologist (D.L.) based on judgement of the patient's degree of awareness on each item after an interview with the patient and the primary caregiver.

Response inhibition task assessment

Patients were asked to perform a response inhibition paradigm (go/no-go task, adapted from Braver *et al.*, 2001) (Fig. 1). They viewed single uppercase letters, presented centrally in Times 24 point font, black on a white background. Each stimulus appeared for 250 ms, followed by a 1000 ms inter-trial interval. Patients had to re-frain from responding to infrequent no-go stimuli (the letter X = 17% frequency) in the context of responding to frequent go stimuli (non-X letters = 83% frequency). The stimuli were presented in random order. Patients had to respond by pressing a button with their right index finger (all patients were right-handed). Only letters from the Italian alphabet were used in order to avoid confounding factors. The task was repeated twice for familiarization purposes, first at the Martini Hospital and then before the functional MRI evaluation. The task was administered for the third time during the functional MRI session. Less than 3 months elapsed between the neuropsychological evaluation and the functional MRI session.

Neuropsychological and neuropsychiatric assessment

The patients with Alzheimer's disease were assessed with a wide battery of neuropsychological and neuropsychiatric tasks. The MMSE
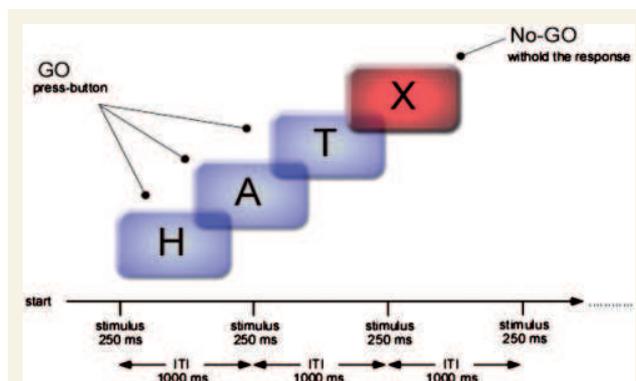

Figure 1 Behavioural task presented to the patients, adapted from Braver *et al.* (2001). Subjects had to respond to 'go' stimuli (the letters 'not-X' with a frequency of 83%) inhibiting the re-sponse to infrequent 'no-go' stimuli (the letter 'X' with a fre-quency of 17%). Every stimulus was shown for 250 ms with a 1000 ms inter-stimulus interval (ITI).

enabled the selection of a homogeneous population. Only patients with scores of 19–24 were selected, as previously suggested by Clare (2004*a*). Alzheimer's disease severity was evaluated using the global deterioration scale (Reisberg *et al.*, 1982). The Alzheimer's dis-ease assessment scale—cognitive subscale (Rosen *et al.*, 1984), the token test for auditory comprehension and the recall of a short story for episodic memory (Spinnler and Tognoni, 1987) were also admin-istered. Trail making parts A, B and the index B–A (Reitan and Wolfson, 1994) were used to measure attention and executive func-tions in terms of cognitive flexibility. Attentional matrices were used to evaluate attentive visual search (Spinnler and Tognoni, 1987). Executive functions were analysed with the behavioural assessment of the dysexecutive syndrome (Wilson *et al.*, 1996). This test is particu-larly useful for detecting executive dysfunction in early Alzheimer-type dementia (Amanzio *et al.*, 2008). It consists of six subscales; for each subscale, a summary profile score can be obtained (range 0–4), the maximum total score being 24. Higher scores indicate better executive functioning.

Perspective-taking abilities were tested using visual theory of mind stories, (as used by Amanzio *et al.*, 2008) to solve problems involving either: first-order attributions of false belief (of the type 'A thinks X') and second-order attributions of false belief (of the type 'A thinks B thinks X'). Each story, administered to patients and caregivers, is fol-lowed by a theory of mind test question and two control questions (memory and comprehension). A total of eight stories were presented to the subjects: four for the first-order false belief test and four for the second-order false belief test. A score of 1 was given for correct an-swers, a score of 0.5 was given for a second attempt at the correct answer and a score of 0 was given for the wrong answer.

The patients were also tested using the HAM-D (Hamilton, 1960), the HAM-A (Hamilton, 1959), the mania assessment scale (Bech *et al.*, 1978; Bech, 2002), the disinhibition scale (Starkstein *et al.*, 2004) and the apathy evaluation scale-informant version (Marin, 1996). Basic and instrumental activities of daily living assessed, respectively, with the Katz *et al.* (1963) and Lawton and Brody (1969) scales, were also considered.

Neuropsychological–neuropsychiatric statistical analysis

Statistical analyses were performed using STATISTICA Software for Windows (version 4.5 Stat Soft Inc., 1993). Differences between aware and unaware patients with respect to the variables of interest were evaluated by means of an independent sample *t*-test. Levene's test was used to test the homogeneity of variances. If homogeneity was violated, results were reported with correction for unequal vari-ances. The chi-square was used to test gender differences. Convergent validity between the overall AQ-D scale and the clinical insight rating scale was verified using Spearman's rho.

Functional MRI assessment

The functional MRI assessment was performed at the CCS functional MRI, Koelliker Hospital in Turin. All participants gave their informed written consent and they were individually instructed on the experi-mental task before entering the scanner.

During scanning, each patient performed four runs of the response inhibition task (Fig. 1). During each run, the two stimulus types (X and non-X) were presented in random order in a continuous series of 232 trials. Each run lasted 290 s. The paradigm was generated using E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA,

USA). The stimuli were presented through a colour LCD video display and projected onto a rear-projection screen in the bore of the magnet; this screen was viewed by the patients via an angled mirror system. The stimuli were presented using the IFIS-SA^{TM} system (MRI Device Corporation, Waukesha, WI, USA) that synchronizes stimulus presentation and functional MRI scanning.

After scanning, each patient was asked to provide an estimate on the number of errors made in the experimental session.

Image acquisition and data analysis

Data acquisition was performed on a 1.5 T INTERA^{TM} scanner (Philips Medical Systems) with a SENSE high-field, high-resolution (MRIDC) head coil optimized for functional imaging. Functional T$_2$-weighted images were acquired using echoplanar sequences, with a repetition time of 2500 ms, echo time of 60 ms and 90° flip angle. The acquisition matrix was 64 × 64 and the field of view was 256 mm. A total of 103 volumes were acquired for each run. Each volume consisted of 16 axial slices, parallel to the anterior–posterior commissure line and covering the whole brain; slice thickness was 6 mm with a 0.5 mm gap. Two scans were added at the beginning of functional scanning and the data discarded to reach steady-state magnetization before acquisition of the experimental data.

In the same session, a set of 3D high-resolution T$_1$-weighted structural images were acquired for each participant. This data set was acquired using a fast field echo sequence, with a repetition time of 25 ms, the shortest echo time and a 30° flip angle. The acquisition matrix was 256 × 256 and the field of view was 256 mm. The set consisted of 160 sagittal contiguous images covering the whole brain. In-plane resolution was 1 × 1 mm and slice thickness was 1 mm (1 × 1 × 1 mm voxels).

Imaging data were analysed using Brain Voyager QX (Brain Innovation, Maastricht, Holland). Each subject's functional data were preprocessed as follows: (i) mean intensity adjustment corrected the global intensity of the repeatedly measured images of a slice: for each slice, the average intensity across the first image was computed; for each subsequent scan of the same slice, the mean intensity was computed and then scaled to result in the same average slice intensity; (ii) 3D motion correction adjusted small head motions: all volumes were aligned spatially to the first volume by rigid body transformations, using a trilinear interpolation algorithm; (iii) slice scan time correction allowed a whole volume to be treated as a single data point: the sequentially scanned slices comprising each volume were interpolated in time, using a signal sinc-interpolation algorithm; (iv) spatial data smoothing was performed using a 3D Gaussian kernel with full-width half maximum of 8 mm; and (v) temporal filters removed drifts due to scanner and physiological noise: linear and non-linear trend removal through a temporal high pass filter eliminating frequencies lower than three cycles in time course were performed.

After pre-processing, a series of steps were followed in order to allow for precise anatomical locations of brain activity to facilitate inter-subject averaging. First, each subject's slice-based functional scans were coregistered to their 3D high-resolution structural scan. This process involved a mathematical coregistration exploiting slice positioning stored in the headers of the raw data, as well as fine adjustments computed by comparing the data sets on the basis of their intensity values; when needed, manual adjustments were also performed. Second, the 3D structural data set of each subject was transformed into Talairach space (Talairach and Tournoux, 1988): the cerebrum was translated and rotated into the anterior–posterior

commissure plane and then the borders of the cerebrum were identified. Third, using the anatomical–functional coregistration matrix and the determined Talairach reference points, the functional time course of each subject was transformed into Talairach space and the volume time course was created.

The following procedure was used to compute voxel-wise group analyses. A multi-subject design matrix was specified and each defined box-car was convolved with a predefined haemodynamic response function to account for the haemodynamic delay (Boynton *et al.*, 1996). A statistical analysis using the general linear model with separate subject predictors was performed on the group to yield random effect functional activation maps of the 'no-go minus go' conditions. A contrast between unaware and aware patients was performed to compare functional activations between groups. All statistical comparisons were made on z transformed scores and were computed at a statistical threshold of $P < 0.05$ corrected for multiple comparisons using false discovery rate correction (Benjamini and Hochberg, 1995). Activated clusters were determined through the automated routines in Brain Voyager and the statistical values for the local maxima of each region were calculated. Anatomical structures were labelled using the Talairach Daemon (Lancaster *et al.*, 1997, 2000), a digitalized version of the Talairach atlas, available online at: http://ric.uthscsa.edu/resources/talairachdaemon.

Following our specific hypothesis regarding the role of the anterior cingulate cortex during the response inhibition task, we also computed a random effect region of interest analysis on this region: within the anterior cingulate cortex we selected a volume of interest encompassing the cingulate zone that has been shown to be specifically activated during tasks that require response selection and wilful generation of motor behaviour (Picard and Strick, 1996; Braver *et al.*, 2001). This subregion of the anterior cingulate cortex is located posterior to the genu of the anterior cingulate cortex, anterior to the vertical plane passing through the anterior commissure (vAC in the Talairach atlas) and superior to the corpus callosum. We operationally defined the locations of the volume of interest as $y = 6 \pm 9$ mm [mean ± standard deviation (SD)], and $z = 40 \pm 9$ mm. Within this volume of interest a multi-subject general linear model with separate subject predictors (unaware versus aware patients) was computed.

Correction for multiple comparisons

In this study we used a recently implemented approach based on a 3D extension of the randomization procedure described in Forman *et al.* (1995) for multiple comparison correction as suggested by Goebel *et al.* (2006). First, a voxel-level threshold was set at t corresponding to a $P < 0.01$ uncorrected. Thresholded maps were then submitted 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. After 2000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate (alpha) of 5% was applied to the statistical maps. The implemented method corrects for multiple cluster tests across space. For each simulated image, all 'active' clusters in the imaged volume were considered and used to update a table reporting the counts of all the clusters above this threshold for each specific size. After a suitable number of iterations (e.g. 2000), an alpha value was assigned to each cluster size based on its observed relative frequency. From this information the minimum cluster size threshold was specified in order to yield a cluster-level false-positive rate of five.

Results

Evaluation of reduced awareness of deficits and neuropsychological–neuropsychiatric assessment

Tables 1–3 show data for the overall Alzheimer's disease population and for patients with Alzheimer's disease divided into two groups according to the presence or absence of awareness. Fifteen patients were classified as 'aware' and 14 were classified as 'unaware' using the AQ-D scale (Migliorelli *et al.*, 1995). Aware and unaware patients did not differ in terms of age, age of dementia onset, education, level of cognitive impairment, comprehension of oral language, episodic memory (recall of a short story), behavioural assessment of the dysexecutive syndrome or on perspective-taking tasks.

Table 3 shows the attentional data for the overall Alzheimer's disease population and for the aware and unaware groups. No significant differences were obtained in the attentional matrices task, nor in trail making task B–A. In contrast, the aware group performed better on the trail making part A and B separately.

Importantly, here we also demonstrated the homogeneity of the two groups of patients in terms of the global deterioration scale (they all obtained a score of 3 attesting mild cognitive impairment). In contrast, the two groups differed for duration of disease in terms of a longer mean duration (of ~10 months) among unaware patients. Table 2 also reports the level of awareness of deficits using the different parts of the AQ-D: the overall AQ-D scale, the cognitive and behavioural parts and the clinical insight rating scale. Convergent validity between the overall AQ-D scale and the clinical insight rating scale was high ($r_{rho} = 0.808$, $P < 0.000001$) indicating that the two unawareness coding processes measured the same phenomenon to a high extent.

As regards neuropsychiatric assessment, the unaware group had higher scores on the disinhibition scale (Table 2). The results of the apathy evaluation scale-informant version and HAM-D evidenced a greater presence of apathy in unaware patients. The hypomania level (mania assessment scale score) was also higher among unaware patients as compared to aware ones, although all patients were below cut-off values. Unaware patients were also marginally more anxious than aware ones (HAM-A scores). No differences were observed in instrumental and basic activities of daily living.

Response inhibition task

Behavioural data of one unaware patient were not recorded due to technical problems. Consequently, functional MRI analyses were conducted on 15 aware and 13 unaware patients.

Table 1 Data from patients with Alzheimer's disease and caregivers

	Alzheimer's disease (n = 29)	Caregivers (n = 29)	t- or χ^2-scores; P-values	Aware (n = 15)	Unaware (n = 14)	t- or χ^2-scores; P-values
Demographic data						
Age (years)	75.03 (5.48)	73.41 (5.87)	NS	74.47 (6.15)	75.64 (4.81)	NS
Education (years)	7.62 (3.39)	8.14 (4.06)	NS	8.13 (2.97)	7.07 (3.83)	NS
Gender (female/male)	17/12	16/13	NS	9/6	8/6	NS
Cognitive assessment						
MMSE [30]	22.38 (2.09)	27.52 (1.97)	$t = -9.61$; $P < 0.000001$	22.53 (2.20)	22.21 (2.04)	NS
Theory of mind assessment						
Theory of mind-first type [4]	3.15 (1.13)	3.76 (0.37)	$t = -2.74$; $P = 0.008$	3.33 (0.97)	2.96 (1.28)	NS
Theory of mind-first type: comprehension	3.45 (0.91)	3.62 (0.49)	NS	3.20 (1.08)	3.71 (0.61)	NS
Theory of mind-first type: memory	3.69 (0.60)	4 (0)	$t = -2.77$; $P = 0.008$	3.60 (0.74)	3.78 (0.42)	NS
Theory of mind-second type [4]	2.45 (1.46)	3.46 (0.46)	$t = -3.56$; $P = 0.0007$	2.80 (1.31)	2.07 (1.58)	NS
Theory of mind-second type: comprehension	3.19 (0.75)	3.34 (0.48)	NS	3.17 (0.86)	3.21 (0.64)	NS
Theory of mind-second type: memory	3.65 (0.55)	4 (0)	$t = -3.36$; $P = 0.001$	3.73 (0.46)	3.57 (0.65)	NS
Mood orientation assessment						
HAM-D [67]	5.86 (3.53)	6.52 (1.86)	NS	4.07 (2.79)	7.78 (3.28)	$t = -3.29$; $P = 0.003$
HAM-A [56]	7.17 (3.32)	5.83 (2.38)	NS	5.87 (2.20)	8.57 (3.80)	$t = -2.37$; $P = 0.02$

The patients with Alzheimer's disease were divided into two groups with reference to the awareness of deficits AQ-D scores (mean ± SD). Maximum scores of the tests are shown in square parentheses. Significant results are expressed in *t*- or χ^2-scores (for gender differences) and *P*-values. MMSE: lower scores indicate more severe cognitive impairment (cut-off ⩽24).
Theory of mind tasks: higher scores indicate better performance.
HAM-A: cut-off ⩾14; HAM-D cut-off ⩾8; higher scores indicate more severe symptoms.
NS = not significant.

Table 2 Patients with Alzheimer's disease

	Alzheimer's disease (n = 29)	Aware Alzheimer's disease (n = 15)	Unaware Alzheimer's disease (n = 14)	t-scores; P-values
Demographic and clinical data				
Duration of illness (months)	27.41 (15.62)	21.80 (12.95)	33.43 (16.42)	t = −2.12, P = 0.04
Dementia onset	72.72 (5.44)	72.60 (6.36)	72.86 (4.49)	NS
Awareness of deficits assessment				
AQ-D overall [90]	21.34 (17.50)	5.67 (5.86)	38.14 (5.92)	t = −14.83; P < 0.000001
AQ-D cognitive part [66]	16.62 (13.47)	4.53 (4.19)	29.57 (4.73)	
AQ-D behavioural part [24]	4.62 (4.95)	1.13 (2.92)	8.36 (3.81)	
Clinical insight rating scale [8]	3.52 (2.06)	1.93 (1.03)	5.21 (1.42)	t = −7.14; P < 0.000001
Cognitive assessment				
Alzheimer's disease assessment scale-cognitive subscale [70]	20.21 (5.84)	19.02 (4.90)	21.48 (6.65)	NS
Recall of a short story [16]	2.36 (1.61)	2.07 (1.55)	2.68 (1.67)	NS
Token test [36]	28.87 (3.49)	28.70 (3.72)	29.07 (3.35)	NS
Behavioural assessment of the dysexecutive syndrome [24]	10.17 (3.49)	10.33 (3.58)	10 (3.51)	NS
Neuropsychiatric and activities of daily living assessment				
Disinhibition scale [96]	9.41 (7.82)	5.07 (5.69)	14.07 (7.19)	t = −3.75; P = 0.0008
Apathy evaluation scale-informant version [54]	28.59 (16.72)	13.33 (4.73)	44.93(4.66)	t = −18.09; P < 0.000001
Mania assessment scale [44]	2.17 (2.04)	1.40 (1.45)	3.00 (2.29)	t = −2.26; P = 0.03
Activities of daily living [6]	5.76 (0.51)	5.87 (0.35)	5.64 (0.63)	NS
Instrumental activities of daily living [8]	5.59 (2.04)	5.93 (2.09)	5.21 (2.01)	NS

Data for patients with Alzheimer's disease (mean ± SD scores) divided into two groups with reference to the awareness of deficits (AQ-D scores). Maximum scores of the tests are shown in square parentheses. Significant results are expressed in t-scores and P-values. Alzheimer's disease assessment scale-cognitive subscale higher scores indicate more severe cognitive impairment; cut-off ⩾14. Recall of a short story, token test and behavioural assessment of the dysexecutive syndrome tests, higher scores indicate better performance; cut off values ⩽4.50, ⩽26.25 and ⩽12, respectively.
Disinhibition scale cut-off ⩾16.9; apathy evaluation scale-informant version, cut-off ⩾43; and mania assessment scale, cut-off ⩾15; higher scores indicate more severe symptoms.
For activities of daily living and instrumental activities of daily living, higher scores indicate better performance.

Table 3 Attentional data for the Alzheimer's disease sample

	Alzheimer's disease (n = 29)	Aware Alzheimer's disease (n = 15)	Unaware Alzheimer's disease (n = 14)	t-scores; P-values
Functional MRI session				
Response inhibition task: Go				
Percent target	85.38 (14.11)	83.69 (13.97)	87.36 (14.69)	NS
RT (ms)	448.85 (75.78)	450.79 (64.6)	446.56 (90.97)	NS
Percent errors	14.62 (14.11)	16.31 (13.97)	12.64 (14.75)	NS
Response inhibition task: No-go				
Percent target	86.52 (14.5)	89.15 (7.47)	82.55 (19.77)	NS
Percent errors	13.48 (14.49)	10.85 (7.47)	16.55 (19.92)	NS
Neuropsychological assessment				
Trail making test form A [500]	115.07 (58.72)	90.47 (35.06)	141.43 (68.25)	t = −2.55; P = 0.02
Trail making test form B [500]	416.07 (140.23)	362.93 (153.59)	473.00 (101.02)	t = −2.26; P = 0.03
Trail making test form B–A	298.83 (120.44)	268.27 (131.80)	331.57 (101.50)	NS
Attentional matrices [60]	34.79 (11.03)	35.87 (12.11)	33.64 (10.07)	NS

Data (mean ± SD scores) is divided into two groups with reference to the awareness of deficits (AQ-D scores). Maximum scores of the tests are shown in square parentheses. Significant results are expressed in t-scores and P-values. Trail making task A, cut-off ⩾94; trail making task B, cut-off ⩾283; and trail making task B–A, cut-off ⩾187; higher scores indicate worse performance. For attentional matrices (cut-off ⩽30), higher scores indicate better performance. NS = not significant; RT = reaction time.

As reported in Table 3, no significant differences were obtained in the response inhibition task. The percentage of correct go and no-go answers in this task did not differ between groups during either the familiarization sessions or the functional MRI sessions.

As far as the estimate on the number of errors committed during the functional MRI session and the actual number made is concerned, we observed a positive correlation in the aware group (r = 0.656; P = 0.018), but not in the unaware group (r = 0.208; P = 0.626).

Table 4 Functional MRI results for the 'no-go' minus 'go' conditions, in the comparison between aware (*n* = 15) minus unaware (*n* = 13) patients

	x	y	z	Cluster size	t
Bilateral rostral prefrontal cortex [10]	−7	54	5	539	2.6
Right postcentral gyrus [2]	47	−23	49	1470	3
Right middle temporal gyrus [39]	41	−71	25	3227	3.9
Right anterior cingulate [24]	10	36	3	389	2.7
Right anterior cingulate [24]	8	23	26	252	2.3
Left temporal gyrus [21]	−42	10	−34	261	2.4
Left middle temporal gyrus [21]	−54	3	−31	747	3.1
Left superior temporal gyrus [38]	−57	13	−16	627	3.5
Right putamen	22	4	3	454	2.7
Left medial globus pallidus	−11	2	1	2251	3.8
Bilateral cerebellum, posterior lobe	−3	−46	−36	1726	3.2
Right cerebellum, anterior lobe	26	−53	29	398	2.9

The table indicates the Talairach coordinates of local maxima of cortical and cerebellar structures showing significant activity *q* < 0.05 cluster-level corrected using a Monte Carlo simulation (refer to the 'Materials and methods' section for further details). Clusters of differential activation (aware–unaware patient group). Square brackets refer to Brodmann areas.

Neuropsychological, neuropsychiatric and perspective-taking assessment of patients and their caregivers

Table 1 also provides the demographic and cognitive data of the overall sample of patients with Alzheimer's disease and their caregivers. There were no significant differences between the two groups with respect to age, level of education, sex and level of anxiety and depression on the HAM-A and HAM-D scales. The caregivers showed no pathological depressive or anxious symptomatology and no cognitive impairment considering the MMSE scores, supporting the conclusion that their judgement of patients' abilities was not biased for any reason. The Alzheimer's disease group achieved low scores on the HAM-D, HAM-A, mania assessment scale, activities of daily living and instrumental activities of daily living scales, attesting a low level of depression, anxiety, mania and low functional disabilities.

The perspective-taking assessment revealed differences between the Alzheimer's disease group and the caregivers (Table 1). In particular, the patients with Alzheimer's disease were more impaired in theory of mind first- and second-type tasks. Indeed, the caregivers performed these tasks perfectly, demonstrating a good ability to make inferences about another individual's mental state.

Imaging data

Important differences emerged when comparing aware versus unaware patients considering the 'no-go' minus 'go' conditions. In particular, the results revealed a series of clusters of activation, as shown in Table 4. The table indicates the Talairach coordinates of local maxima of cortical and cerebellar structures showing significant activity (*P* < 0.05, corrected for multiple comparisons).

The unaware patients showed reduced task-sensitive activity in the rostral prefrontal cortex (bilaterally), in the right anterior cingulate cortex, post-central gyrus, middle temporal gyrus and putamen, as well as in the left middle and superior temporal gyrus and medial globus pallidus. Besides in the cerebellum, lower activations were detected in the bilateral posterior lobe and in the right anterior lobe of unaware patients. Table 4 indicates the Talairach coordinates of the local maxima of such differential activations (*P* < 0.05, corrected for multiple comparisons). Figure 2 shows such activations on a 3D cortex reconstruction; Supplementary Fig. 1 shows the same activations on axial slices.

The random effect (region of interest) analysis performed on the cingulate area using the general linear model revealed a significant difference between groups (aware versus unaware patients), *P* < 0.026, *t* = 2.343. Figure 3 shows the percentage of the blood-oxygen-level-dependent signal change in the anterior cingulate cortex region of interest for the 'no-go' condition, for the aware and unaware patients.

The clusters of activations found in aware and unaware patients, respectively, in the 'no-go' minus 'go' conditions are shown in Supplementary Fig. 2. The aware patients showed greater right-lateralized activations (Supplementary Fig. 3). In contrast, the unaware patients had a reduced task-sensitive activity in the cingulate area, in the rostral prefrontal cortex and striatum (Supplementary Fig. 3). Supplementary Fig. 4 shows the synopsis of the functional MRI results for the 'no-go' minus 'go' conditions and the differential activations in comparison between aware and unaware patients, and shows areas of greater activation in the unaware group. The Talairach coordinates of local maxima of cortical and cerebellar structures showing significant activity for the 'no-go' minus 'go' conditions, in the comparison between aware minus unaware patients are reported in Supplementary Table 1.

Discussion

Our results show that unawareness of deficits in early Alzheimer's disease is associated with reduced functional recruitment of the cingulofrontal and parietotemporal regions during a response inhibition task. Moreover, our findings show that apathy and
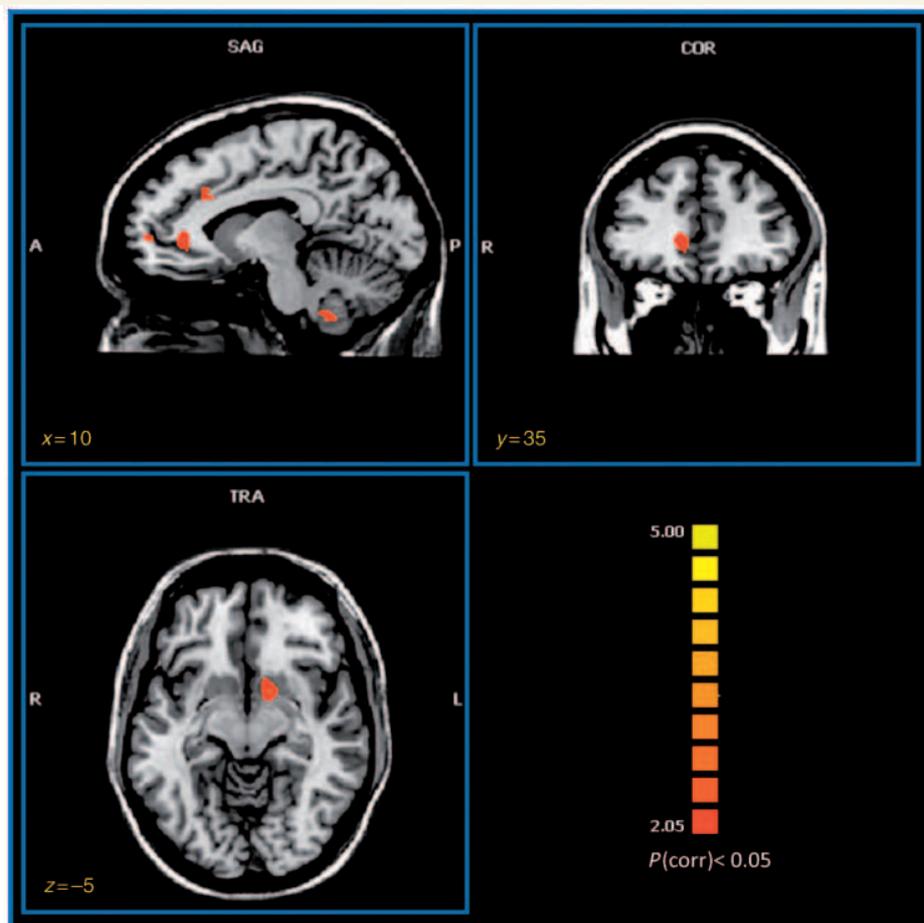
Figure 2 Functional MRI results for the 'no-go' minus 'go' conditions, in the comparison between aware ($n = 15$) minus unaware ($n = 13$) patients. Maps were thresholded at $q < 0.05$ cluster-level corrected using a Monte Carlo simulation (refer to the Materials and methods section for further details). Maps are projected on a 2D brain surface with Brain Voyager QX 2.1. Cor = coronal; sag = sagittal; tra = transverse.

disinhibition appear as the first significant behaviour changes in unaware subjects.

In the first part of this section, the functional MRI results are discussed, with special emphasis the role of the cingulofrontal and parietotemporal convergence regions in the phenomenon of unawareness. The role of specific neuropsychiatric and neuropsychological changes in the unawareness of our patients with Alzheimer's disease is then addressed. Lastly, the procedures followed to control the validity of awareness measurement are discussed.

Interestingly, the comparison of functional activations between groups (Table 4 and Figs 2 and 3 and Supplementary Figure 3) highlighted reduced task-sensitive activity in cingulate area (Brodmann area 24) and in Brodmann area regions 10 and 39, of the right hemisphere in the unaware group. Vogt and Devinsky (2000) defined these regions as primary processors of the mind, critical for decision-making in relation to the internal/external and motivational parameters of self and essential links in networks engaged by mental activity for processing self-significant information. These areas, among others, are represented in the cingulofrontal (Brodmann areas 24 and 10) and the parietotemporal (Brodmann area 39) confluence regions. The ventromedial frontal cortex and the parietotemporal junction were recently described as playing an important role in the right lateralized ventral attention system [Corbetta and Shulman (2002); for a review see Fox et al. (2006)]. The cingulofrontal confluence region provides the information upon which a response is selected among different motivationally relevant cognitive and behavioural outputs (Vogt and Devinsky, 2000). Activations of the anterior cingulate and dorsolateral prefrontal cortices during a visually guided, divided attention task led Corbetta et al. (1991) to suggest that these two regions are involved in response selection in cognitively challenging situations. Further support for this hypothesis comes from studies which used the Stroop task and demonstrated a task-related activation of the anterior cingulate cortex and of prefrontal areas such as Brodmann area 10 (Pardo et al., 1990; Bush et al., 1998; Derbyshire et al., 1998). Our functional MRI results suggest a reduced activation in unaware subjects of those areas
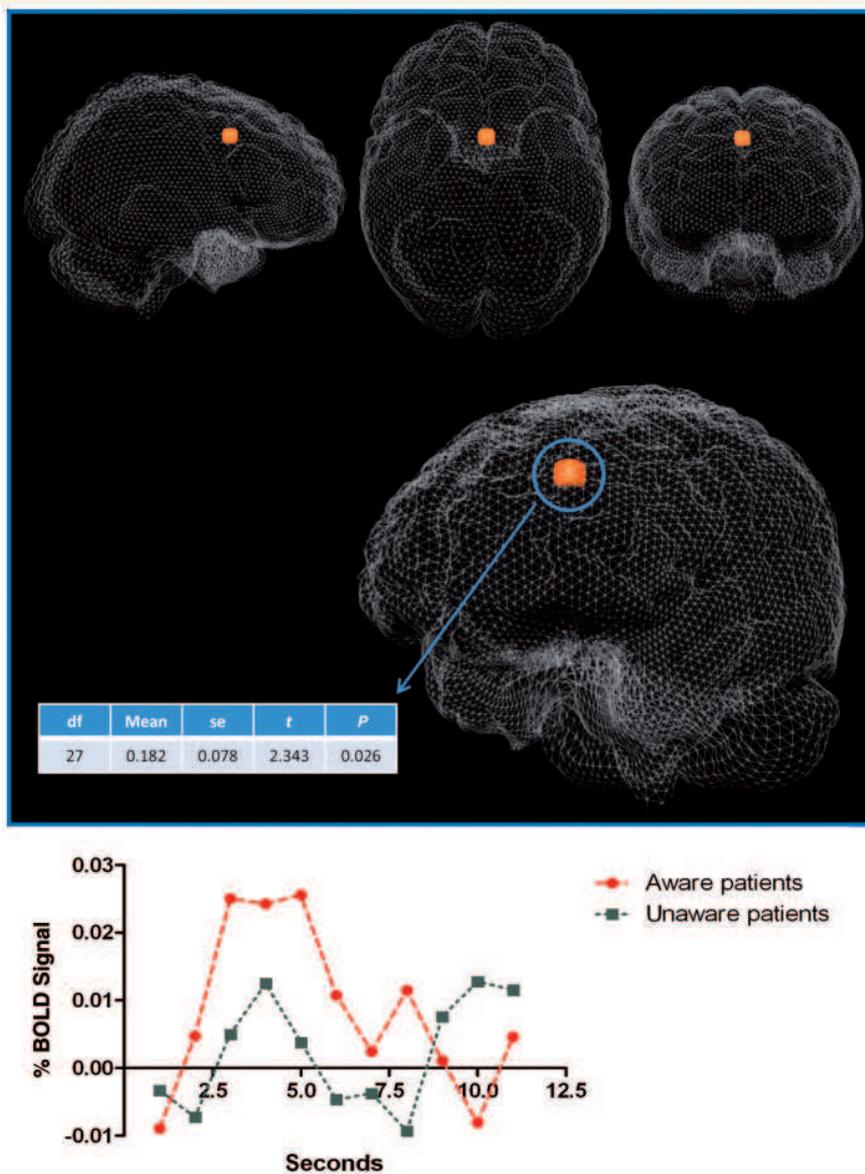
df	Mean	se	t	P
27	0.182	0.078	2.343	0.026

Figure 3 Functional MRI results for the 'no-go' minus 'go' conditions, in the comparison between aware (*n* = 15) minus unaware (*n* = 13) patients. *Top*: maps were thresholded at *q* < 0.05 cluster-level corrected using a Monte Carlo simulation (refer to the Materials and methods section for further details). Maps are projected on a 3D brain surface with Brain Voyager QX 2.1. Arrows indicates the results of the region of interest analysis performed on the anterior cingulate cortex area. *Bottom*: percentage of functional MRI signal change in anterior cingulate cortex region of interest for the 'no-go' minus 'go' conditions, for the aware (red line) and unaware (grey line) patients. BOLD = blood-oxygen-level-dependant.

involved in conflict monitoring that are usually activated when a choice has to be made between two incompatible responses that are both compelling (Supplementary Fig. 2). Monitoring such occurrences is necessary to provide feedback as to when strategic processes must be more strongly engaged to adapt ongoing behaviour. As far as the parietotemporal confluence region is concerned, hypometabolism and reduced cerebral blood flow in the parietotemporal association areas constitute the most consistent metabolic findings in patients with Alzheimer's disease (Duara *et al.*, 1986; Jagust *et al.*, 1990). It is possible that following the dysfunction of the parietotemporal association areas, further

disruption of blood flow that is restricted to the right frontal lobe may produce the unawareness of deficits in our patients with early Alzheimer's disease. Moreover, previous studies using go/no-go tasks have shown that the neural networks associated with inhibitory processing include not only the cingulofrontal convergence region, with the anterior cingulate cortex playing the main role, but other areas also involved in our paradigm, such as the parietal and temporal lobes and the striatal regions (Kawashima *et al.*, 1996; Casey *et al.*, 1997; Garavan *et al.*, 1999; Konishi *et al.*, 1999; Kiehl *et al.*, 2000; Liddle *et al.*, 2001; Rubia *et al.*, 2001; Chikazoe *et al.*, 2007; Nakata *et al.*,

2008). Such neural networks are not dependent on sensory modalities, but reflect common neural activities specific to inhibitory processing (Nakata *et al.*, 2008). Our results show a clear lateralization in the afore-mentioned areas. Indeed they point to a specific role of the right hemisphere in the awareness of deficits. These findings are in line with previous studies on unawareness in Alzheimer's disease that emphasized the importance of frontal and temporoparietal areas and of the right hemisphere in general. In detail, Reed *et al.* (1993) reported that patients with 'full awareness' showed significantly higher perfusion in the right dorsolateral prefrontal cortex, compared to those with 'shallow awareness' or 'no awareness'. Starkstein *et al.* (1995) found a relationship between blood-flow hypoperfusion in the frontal inferior and superior (dorsal) areas of the right hemisphere and unawareness. Ott *et al.* (1996) hypothesized a relationship between unawareness and frontal right hemisphere dysfunctions. Vogel *et al.* (2005) found a significant correlation between unawareness and reduced cerebral blood flow in the right inferior frontal cortex, concluding that the right inferior gyrus was crucial for awareness. Harwood *et al.* (2005) found unawareness to be related with dysmetabolism in a focal region of the right prefrontal cortex. Mimura and Yano (2006) also found a significant correlation between unawareness of memory disturbances and reduced cerebral blood flow in bilateral frontal regions. More recently, Shibata *et al.* (2008) found a significant association between unawareness and reduced cerebral blood flow in the ventromedial prefrontal cortex (orbitofrontal regions). Hanyu *et al.* (2008), studying the correlation between unawareness of memory deficits and cerebral perfusion on single photon emission computed tomography in early Alzheimer's disease, found functional damage to the inferior, medial and orbital frontal lobes as well as the anterior cingulate gyri in unaware patients.

While these studies provide a first important insight into the neural substrates of unawareness in Alzheimer's disease, they also have several limitations. In some, the diagnosis of unawareness was only based on a psychologist's clinical impression and no structured assessments were carried out (Reed *et al.*, 1993; Vogel *et al.*, 2005). This left the lack of awareness in other cognitive areas beyond memory loss unstudied and did not take into account the unawareness of behavioural problems. No anxiety scales were administered to patients (Starkstein *et al.*, 1995) and in certain cases depressive symptomatology also was not measured (Vogel *et al.*, 2005; Hanyu *et al.*, 2008; Shibata *et al.*, 2008). In those studies in which caregivers were asked to judge patients' abilities, no perspective-taking measurements were administered to them to exclude disabilities in making inferences about another individual's mental states (Starkstein *et al.*, 1995; Salmon *et al.*, 2005; Vogel *et al.*, 2005; Hanyu *et al.*, 2008; Shibata *et al.*, 2008). No assessments of anxiety and depressive mood levels were collected for caregivers as well (Starkstein *et al.*, 1995; Salmon *et al.*, 2005; Vogel *et al.*, 2005; Hanyu *et al.*, 2008; Shibata *et al.*, 2008). Thus, a possible bias in caregivers' judgments was not properly excluded. In some of these studies, relatively small samples of patients were included (Reed *et al.*, 1993) and differences in memory, executive performance and depression severity were not controlled (Shibata *et al.*, 2008). In certain cases, patients appeared more impaired than ours, having moderate or

severe severity of dementia (Starkstein *et al.*, 1995), or the range in terms of MMSE appeared too large, leaving the doubt that patients with mild cognitive impairment had also been included (range: 10–28 as in the study of Salmon *et al.*, 2005). Patients were also treated with donepezil leaving a possible influence of cholinesterase inhibitors on awareness and mood conditions uncontrolled (Salmon *et al.*, 2006; Hanyu *et al.*, 2008). Most importantly, these studies leave the important link between response inhibition disabilities and unawareness of deficits in patients with Alzheimer's disease during functional MRI sessions unexplored. It has been hypothesized that some patients with Alzheimer's disease may suffer from a form of unawareness in which the deficit arises in comparator mechanisms neurally instantiated in the frontal lobes (Morris and Hannesdottir, 2004; Hannesdottir and Morris, 2007). These comparator mechanisms may function at different levels (both as domain-specific and global comparators) and be responsible for monitoring performance. Each individual comparator monitors performance on cognitive tasks and uses this information to adjust future behaviours. If there is a problem at the level of the comparator mechanisms, there is no monitoring of signal error and the meaning of failure is lost. In this executive unawareness a faulty appreciation of performance, with no recognition of failure, leads to a lack of update of the patient's personal database. Even if these theorizations about unawareness in Alzheimer's disease were more associated with memory related cognitive tasks, we believe response inhibition abilities may constitute a fruitful approach for studying differences in the awareness of deficits in patients with early Alzheimer's disease, supported by the demonstration of an association between response inhibition disabilities and unawareness of deficits in patients with Alzheimer's disease using a neuropsychological approach (Kashiwa *et al.*, 2005). In particular, if the comparator mechanism of monitoring attentive performance is compromised at a prefrontal striatal level, patients lose the ability to recognize their disturbances and errors not only in an environmental setting but also during the test session. Indeed, only aware patients were able to correctly judge the number of errors made in the functional MRI session.

The comparison of aware versus unaware patients with Alzheimer's disease showed that the two groups performed with similar accuracy on the response inhibition task during the functional MRI session. The reduced brain activation in task-related areas observed in unaware patients, might have triggered a compensation mechanism and thus recruitment of additional neural resources. This additional recruitment might have positively contributed to the behavioural performance. In particular, we demonstrated right lateralized posteromedial parietal area activations greater in unaware patients (Supplementary Figs. 2 and 4, Supplementary Table 1).

As regards the neuropsychological and neuropsychiatric assessments, in line with previous findings (Starkstein *et al.*, 1996) our results show that, in unaware patients, apathy and disinhibition are prominent features of the first behavioural changes. Other studies have described the presence of behavioural and psychiatric symptoms in patients with unawareness (Lopez *et al.*, 1994; Michon *et al.*, 1994; Migliorelli *et al.*, 1995; Harwood *et al.*, 2005; Vogel *et al.*, 2005). Our unaware patients obtained higher

scores on the apathy evaluation scale-informant version and HAM-D scales; these results suggest the presence of apathetic symptoms. The HAM-D scale actually measures changes not only in terms of depressive mood but also of apathetic behaviour (Assal and Cummings, 2002). The apathy evaluation scale-informant version is a specific instrument for assessing apathy in patients with Alzheimer's disease (Clarke *et al.*, 2007). Starkstein *et al.* (1996) found that cognitive unawareness was related to apathy and, in a more recent study, Starkstein *et al.* (2001) showed that the severity of dementia and apathy were both significantly associated with unawareness of deficits in Alzheimer's disease. In another longitudinal study, Starkstein *et al.* (2006) found that apathy is a behavioural marker of a more aggressive Alzheimer-type dementia, characterized by a faster progression of cognitive, functional and emotional impairment.

In patients with Alzheimer's disease, the variability of morpho-functional alterations, the degree of prefrontal lobe impairment and right side cortical involvement (medial prefrontal cortex, and dorsal and ventral anterior cingulate cortices) are responsible for the different expression, intensity and onset time of apathetic behaviour (Migneco *et al.*, 2001; Levy and Dubois, 2006; Marshall *et al.*, 2007) and apathy is a prominent feature of behavioural changes in early Alzheimer's disease (Starkstein *et al.*, 2001, 2007). The cingulate monitoring hypothesis in apathy (Cohen *et al.*, 2000) indicates that the anterior cingulate cortex is part of an executive control network that works together with the prefrontal dorsolateral cortex to ensure coordinated goal-directed behaviour. Accordingly, it has been demonstrated that apathetic patients with Alzheimer's disease are less attentive to their surroundings as well as to their needs and emotions (Marin *et al.*, 1991).

Starkstein *et al.* (1996), suggested that unawareness of behavioural problems may be part of a disinhibition syndrome, wherein the loss of inhibition of socially inappropriate behaviour may occur. The authors further suggested that scores on disinhibition scales increase as the disease progresses (Starkstein *et al.*, 2004). Although our unaware patients obtained higher scores on the disinhibition scale, the Alzheimer's disease subgroup with reduced awareness of deficits should not be clinically considered as having disinhibited behaviour; none presented psychiatric symptoms such as mania (even though we observed a significant difference through the mania assessment scale between the two groups, no patients obtained scores above the cut-off value on this scale), delusions or hallucinations and none were being treated with psychotropic drugs. These results suggest that an early mild change in behaviour occurs in the unaware subgroup and that this should not be considered as relevant from a psychopathological point of view.

In the literature, there are discrepancies about the association between unawareness of deficits and executive dysfunctions, with some authors finding no such association (Reed *et al.*, 1993; Migliorelli *et al.*, 1995; Starkstein *et al.*, 1996; Hannesdottir and Morris, 2007). In contrast, various studies have shown that the lack of awareness may be marked by specific executive function disabilities related to self-monitoring, flexible thinking and inhibition of a dominant response (Lopez *et al.*, 1994; Michon *et al.*,

1994; Kashiwa *et al.*, 2005). This discrepancy could be due to: (i) the use of different methods to assess the awareness of mental impairment in patients with Alzheimer's disease and the presence of only a few studies that consider the two different domains of cognitive and behavioural unawareness (Migliorelli *et al.*, 1995; Starkstein *et al.*, 1996, 2006) or (ii) the failure of traditional frontal lobe tests to reflect cognitive demands of real-life tasks and detect the functionality of the two subcomponents of executive functions referred to dorsolateral and ventromedial prefrontal cortex regions even at an early stage of the disease (Stuss and Levine, 2002).

Our aware and unaware subjects with Alzheimer's disease did not differ in terms of demographic and clinical variables. However, unaware patients showed more severe cognitive flexibility disabilities on trail making task forms A and B separately. This might suggest that an impairment in cognitive flexibility may be a prerequisite for the unawareness of deficits. Importantly, these tests rely to some extent on the ability to inhibit a dominant response. The relationship between unawareness of deficits and the trail-making task has already been demonstrated by Lopez *et al.* (1994) and a recent neuroimaging study has demonstrated that the medial frontal area is involved in the performance of the trail making task part B versus A (Zakzanis *et al.*, 2005).

We hypothesize that hypofunctionality at the ventromedial prefrontal cortex of our unaware patients with Alzheimer's disease causes a deficit in the response inhibition and flexible thinking associated with the awareness of deficits; such disabilities may interfere not only with the awareness of cognitive deficits but also with the awareness of behavioural deficits. In particular, our unaware patients with Alzheimer's disease had difficulty in keeping track of changes in their apathy and disinhibition features, as we observed in the AQ-D. Flexible thinking and the ability to inhibit a response all appear to be important skills for the awareness of everyday cognitive deficits in our Alzheimer's disease population, in line with Kaszniak and Zak (1996) who hypothesized that impaired awareness of deficits in patients with Alzheimer's disease was caused by poor 'on-line' memory self-monitoring, related to frontal lobe dysfunction. Self-monitoring and response inhibition abilities have both been found to be implicated in metacognitive functions. This represents an important link between cognitive dysfunctions and changes in behaviour. Metacognitive processing in fact contributes to the self-regulation of behaviour through central executive functions. This includes how effectively and accurately an individual is able to use self-knowledge and self-monitoring abilities to guide cognition and behaviour in social and non-social contexts (Fernandez-Duque *et al.*, 2000). Self-awareness, as described by Stuss and colleagues (Stuss *et al.*, 2001; Stuss and Anderson, 2004), relies on the frontal lobes and their limbic connections at the level of the ventromedial prefrontal cortex, with the right frontal part playing a crucial role (Stuss *et al.*, 2001). At this level of Stuss' model, self-awareness implies self-reflecting and metacognitive abilities to use one's own experience of mental states, beliefs, attitudes and experiences to understand the mental states of others (Stuss and Anderson, 2004). Without such ability, the world may not be interpreted properly and social misjudgements may occur. In our patients with Alzheimer's disease, a deficit in metacognitive functions makes it difficult for them to update their evaluations of their

own behaviour, as described previously by other authors (McGlynn and Schacter, 1989; Green et al., 1993).

Since quantifying unawareness in patients with Alzheimer's disease can prove difficult, even at an early stage of disease (there is actually no golden standard method for assessing this symptom), we used the only validated method in the literature, AQ-D (Migliorelli et al., 1995), which is able to differentiate between aware and unaware patients based on cut-off values. Since this method is based on a subtractive index between caregivers and patients, excluding any bias in caregivers' judgements is crucial. As reported by some authors, caregivers' ratings may be influenced by variables such as: anxiety and proneness to depressive mood (Jorm, 1992, Ott and Fogel, 1992; Jorm et al., 1994), the severity of the patient's behavioural deficits and state of illness or stress associated with caring for the patient (DeBettignies et al., 1990). For these reasons we controlled for possible bias in our sample. We performed a psychological evaluation to test for and exclude the presence of anxious-depressive subclinical symptomatology in the caregivers. Moreover, we administered the HAM-D and HAM-A scales to all the participants in the study; all caregivers obtained scores below cut-off values with both instruments. This clearly indicates the absence of any pathological depressive and anxious symptomatology. The lack of subclinical symptomatology suggests that the caregivers provided a reliable score. We also ascertained the caregivers' cognitive functions and their ability to make inferences about another person's mental state in perspective-taking tasks. The results showed the caregivers had good abilities in such tasks, further supporting the conclusion that their judgements on patients' abilities were not biased for any reason.

We also requested an experienced neurologist to judge the patients' unawareness of their deficits using the clinical insight rating scale (Ott and Fogel, 1992; Ott et al., 1996). In this way we were able to reliably divide the patients into groups. Indeed, agreement between the two instruments was very high. Looking for a convergence of perspectives would actually be another possible way of compensating for limitations in the validity of awareness measurement (Snow et al., 2004).

As far as the homogeneity of the patients is concerned, we followed the indications of Clare (2004a) who suggested that Alzheimer's disease studies should include subjects with an MMSE score ranging from 19 to 24, corresponding to a mild stage of cognitive impairment, since it is unclear how the same assessment methods used in Alzheimer's disease unawareness studies could be fully appropriate for patients with very extensive differences in MMSE scores. Importantly, in the study by Hannesdottir and Morris (2007) for example, the authors underlined that the lack of association between unawareness and executive dysfunction might be due to their selection of patients ranging from very mild to moderate Alzheimer's disease. In this case and in other studies (Verhey et al., 1993) assessment of awareness might be invalidated by impairments in language and comprehension (Mullen et al., 1996). We demonstrated the homogeneity of the two groups of patients in terms of the global deterioration scale (all obtained a score of 3 attesting mild cognitive impairment), and in terms of demographic and cognitive variables. These results attested the homogeneous level of mild cognitive impairment and low depressive-anxiety

symptomatology in the two groups. The only difference observed between the groups was in terms of the duration of illness, with a longer duration of ~10 months among unaware patients than among aware ones.

Conclusion

This study of unawareness and its neuropsychological correlates has important clinical implications as this phenomenon can involve diagnostic, nosological and prognostic factors that directly affect treatment adherence. Unawareness is often related to poor clinical outcomes and impaired psychosocial functioning. Unaware patients increase the caregivers' burden as they are unable to track changes in their cognitive and behavioural status, thus requiring additional assistance. We believe that theoretical models of unawareness have greater clinical utility and are more effective if they integrate functional MRI and neuropsychological data, given the relevance of detecting possible psycho-biological markers of this phenomenon in an early phase of Alzheimer-type disease. Importantly, to the best of our knowledge, this is the first study to investigate the relationship between response inhibition disabilities and unawareness of deficits in patients with Alzheimer's disease using a specific executive task (anterior cingulate cortex sensitive) during a functional MRI session. Crucially, previous studies only analysed the differences between aware and unaware patients at an anatomical-functional level using PET and single photon emission computed tomography neuroimaging techniques in resting state conditions. In our study we demonstrated the role, not only of the anterior cingulate cortex and parietotemporal regions, but also of a prefrontal striatal dysfunction of the executive monitoring system that play a particular role in the domain of reduced awareness.

Our data indicate that unaware patients with Alzheimer's disease show functional impairments at the level of the cingulo-frontal confluence region and the ventral system. Furthermore, unaware patients also show additional activations of posteromedial parietal areas that may reflect those compensatory activations that contribute to the maintenance of the performance in the response inhibition task. The posteromedial parietal region shows specific structural and baseline functional changes in early stage Alzheimer's disease (as reviewed in Cavanna, 2007; Dickerson and Sperling, 2009). Interestingly some authors observed a task-induced deactivations of the precuneate cortex when normal subjects are engaging goal-directed cognitive processing (Binder et al., 1999; Gusnard et al., 2001; Mitchell et al., 2003), this observation is in line with the results obtained in the aware patients.

Finally, our results show that unaware patients are more impaired in flexible thinking and demonstrate more pronounced behavioural disinhibition and apathy with respect to aware ones.

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Supplementary material

Supplementary material is available at *Brain* online.

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