NBA-7002; No. of Pages 15 ARTICLE IN PRESS

ELSEVIER

Neurobiology of Aging xxx (2008) xxx–xxx

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Perspective taking to assess self-personality: What's modified in Alzheimer's disease?

Perrine Ruby [a,b], Fabienne Collette [b,c], Arnaud D'Argembeau [b,c], Frédéric Péters [b], Christian Degueldre [b], Evelyne Balteau [b], André Luxen [b], Pierre Maquet [b], Eric Salmon [b,d,*]

[a] *INSERM, U821, 69675 BRON Cedex, France*
[b] *Cyclotron Research Center, University of Liège, B30 Sart Tilman, 4000 Liège, Belgium*
[c] *Experimental Psychology and Cognitive Neuroscience Research Unit, University of Liège, B33 Sart Tilman, 4000 Liège, Belgium*
[d] *Memory Center, Service of Neurology, CHU Liège, B35 Sart Tilman, 4000 Liège, Belgium*

Received 21 June 2007; received in revised form 4 December 2007; accepted 19 December 2007

Abstract

Personality changes are frequently described by caregivers of patients with Alzheimer's disease, while they are less often reported by the patients. This relative anosognosia of Alzheimer disease (AD) patients for personality changes might be related to impaired self-judgment and to decreased ability to understand their caregiver's perspective. To investigate this issue, we explored the cerebral correlates of self-assessment and perspective taking in patients with mild AD, elderly and young volunteers. All subjects assessed relevance of personality traits adjectives for self and a relative, taking either their own or their relative's perspective, during a functional imaging experiment. The comparison of subject's and relative's answers provided congruency scores used to assess self-judgment and perspective taking performance. The self-judgment "accuracy" score was diminished in AD, and when patients assessed adjectives for self-relevance, they predominantly activated bilateral intraparietal sulci (IPS). Previous studies associated IPS activation with familiarity judgment, which AD patients would use more than recollection when retrieving information to assess self-personality. When taking a third-person perspective, patients activated prefrontal regions (similarly to young volunteers), while elderly controls recruited visual associative areas (also activated by young volunteers). This suggests that mild AD patients relied more on reasoning processes than on visual imagery of autobiographical memories to take their relative's perspective. This strategy may help AD patients to cope with episodic memory impairment even if it does not prevent them from making some mind-reading errors.
© 2007 Elsevier Inc. All rights reserved.

Keywords: Alzheimer; Self; Perspective taking; Mind representation; Anosognosia; fMRI; Intraparietal sulcus; Prefrontal cortex

1. Introduction

Alzheimer disease (AD) is a neurodegenerative disease affecting predominantly associative brain regions such as medial temporal cortex, posterior cingulate, lateral temporal, parietal and frontal cortices (Buckner et al., 2005; Herholz et al., 2002; Salmon et al., 2005a,b), and clinically characterized by progressive decline in memory and higher cognitive functions. AD patients are mainly impaired in controlled cognitive processes such as explicit memory recall (Adam et al., 2005; Fabrigoule et al., 1998), and they frequently rely on familiarity-based processes, allowing them to perform routine (automatic) activities (Adam et al., 2005; Dalla Barba, 1997; Rauchs et al., 2007; Westerberg et al., 2006). Moreover, personality changes and impaired judgment are typically observed in the disease (Cummings et al., 1994). An intriguing symptom is the lack of awareness of AD patients (anosognosia) for the clinical changes occurring as

* Corresponding author at: Cyclotron Research Center, University of Liège, B30 Sart Tilman, 4000 Liège, Belgium. Tel.: +32 43662316; fax: +32 43662946.

E-mail addresses: pruby@lyon.inserm.fr (P. Ruby), f.collette@ulg.ac.be (F. Collette), eric.salmon@ulg.ac.be (E. Salmon).

0197-4580/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2007.12.014

neurodegeneration progresses. The degree of anosognosia varies across different clinical domains (Kalbe et al., 2005) and it appears especially salient for cognitive decline, impaired prospective memory and moral judgments in AD (Gil et al., 2001; Vasterling et al., 1997). Lack of awareness has been related to brain dysfunction in various regions, such as the hippocampus (Marshall et al., 2004; Salmon et al., 2006), the temporoparietal junction (Salmon et al., 2006), and the inferior, orbital or superior frontal cortex (Salmon et al., 2006; Vogel et al., 2005). The physiopathology of this symptom remains poorly understood (Vuilleumier, 2004).

One difficulty in the physiopathological research concerning anosognosia is that measuring lack of awareness is a real challenge. Indeed, anosognosia theoretically defines a discrepancy between facts (i.e. impaired behavior, hemiplegia, etc.) and a subjective representation of such facts, which is difficult to measure precisely. Two main methods are commonly used to assess anosognosia, (1) comparison of patient's self-report of cognitive functioning with his performance on objective testing (Souchay et al., 2002) and (2) comparison of patient's self-report with that of a close informant (Derouesne et al., 1999; Migliorelli et al., 1995; Ruby et al., 2007; Salmon et al., 2006). The former can easily be used to measure anosognosia for cognitive deficits but may be less adapted to assess anosognosia in the social and emotional domain. In this later domain indeed, quantifying real life social performances may be quite difficult using laboratory tasks. In the social domain, the second method may thus be useful even if it depends on the reliability and validity of a close informant report. In fact, several results argue in favor of the trustworthiness of the relatives: (1) their reports are generally closer to objective measures than patient self-assessments (DeBettignies et al., 1990; Jorm, 1994) and (2) clinico-metabolic correlations showed that subjective assessment of AD cognitive abilities by their relatives was related to metabolism in posterior and frontal associative areas of the patients, just as objective cognitive evaluation of the patients was (Salmon et al., 2005a,b).

To better understand the different methods used to measure anosognosia, a recent study used positron emission tomography with the 18F-fluorodeoxyglucose method (FDG–PET) to correlate brain activity at rest with two measures of anosognosia in AD: (1) confrontation of subjective and objective assessment of the patient and (2) discrepancy score between patient's and relative's evaluation (Salmon et al., 2006). These two measures were found to have different cerebral correlates. Patient's assessment unconfounded by objective cognitive performances was related mainly to right parahippocampal and orbitofrontal cortex dysfunction, while the discrepancy score inversely correlated with hypometabolism in bilateral temporoparietal junction and inferior temporal cortex. Interestingly, each measure of anosognosia was related to brain regions involved in memory processes (see Marshall et al., 2004), and also to brain regions involved in third-person perspective taking ability in a social and emotional context such as the orbitofrontal cortex and the temporoparietal junction (see Ruby and Decety, 2004). An explanatory hypothesis is that anosognosia for cognitive deficits in AD patients originates both in memory and perspective taking deficits (Salmon et al., 2005b). Our idea in the present study was to extend this hypothesis to anosognosia for self-personality misrepresentation in AD.

This hypothesis fits with previous work conceptualizing the self as a complex knowledge structure that relies on different components such as episodic and semantic memory, and the ability to reflect on one's own thoughts and experience (Klein et al., 2002). Anosognosia for self-personality misrepresentation in AD could, on the one hand, be related to impaired autobiographical memory (Greene et al., 1995; Piolino et al., 2003) and to reliance on familiarity-based judgments (Adam et al., 2005; Westerberg et al., 2006). Accordingly, Rankin et al. (2005) showed that AD patients made a mixture of accurate and inaccurate self-assessments of social abilities depending upon the facet of personality evaluated. For all of these personality facets, the current self-assessments of AD patients closely matched the informant's description of their premorbid personality. The authors concluded that the source of inaccurate self-awareness in AD patients was a failure to update their self-image. In other words, distorted self-representation in AD would originate in familiarity-based reliance on old semantic knowledge, that is not updated due (partly) to deficits in episodic memory and reflective processes. As a consequence, one can expect that during a task requiring recall of autobiographical information for self-assessment, AD patients would not recruit brain regions typically involved in autobiographical memory retrieval in healthy subjects (Addis et al., 2007; Andreasen et al., 1995; Graham et al., 2003; Maguire et al., 1999), and that they would rely on brain regions involved in familiarity-based retrieval more than in recollection (Henson et al., 1999; Ranganath et al., 2004; Yonelinas et al., 2005). On the other hand, anosognosia for self-personality misrepresentation would be related to perspective taking deficits. Reflection on self is a task requiring evaluative processes (Klein et al., 2002; Levine et al., 1999; Wilson and Dunn, 2004), initially performed with a first-person perspective. However, when engaged in reflective processing on the self, a third-person perspective (looking at ourselves through the eyes of others) may be especially useful to update our beliefs on our own personality (Wilson and Dunn, 2004). In other words, information issued from a third-person perspective reasoning on the self may critically participate to the first-person perspective reflection on the self and then to the self-judgment (Gambini et al., 2004; Marcel et al., 2004). The third-person perspective is a constructive process of inferring, related to theory of mind (TOM) or mentalizing (Frith and Frith, 2003). Thus, our hypothesis is that awareness of a "correct/wrong" judgment on the self requires the ability to take into account the perspective of other persons on the self. A patient, in order to assess himself as "rude" for example certainly needs to be able to infer the mind of other persons. Indeed, the adjective "rude" in itself refers to the (embarrassed) reaction you may induce in other persons when acting or speaking. Hence, if a patient cannot infer anymore the mind of others, this necessarily prevents him from realizing that his behavior is "rude" (i.e. provoke embarrassment in others). TOM is impaired in AD patients, possibly be due to various cognitive deficits (Cuerva et al., 2001; Gregory et al., 2002), and impaired third-person perspective taking may participate in anosognosia for self-personality change in AD patients (Salmon et al., 2005b).

To recapitulate, the hypothesis investigated in this study is that anosognosia for behavioral and personality changes in AD originates both in loss of controlled memory processes and in perspective taking deficits (Salmon et al., 2006, 2005a,b). Accordingly, our experiment was designed to assess first- and third-person perspective taking ability in AD during self and other personality trait attribution and to look for their cerebral correlates using functional magnetic resonance imaging (fMRI). The report of a close relative was used as a reference to measure "performance" (congruency scores) in first- and third-person perspective conditions. We hypothesized that due to episodic memory deficit, AD patients would rely on familiarity-related more than on recollection-related brain regions for self-personality traits evaluation (Klein et al., 2003; Rankin et al., 2005). We also anticipated that AD participants would demonstrate third-person perspective taking impairment in personality assessment and we predicted changes in prefrontal activation (associated with modified inferring processes) during perspective taking in AD compared to healthy controls. This prediction was based on previous works concerning memory tasks in AD patients, reporting that executive dysfunction in AD could lead to both decreased recruitment and increased activation in different executive networks (Backman et al., 1999; Becker et al., 1996; Prvulovic et al., 2005).

2. Materials and methods

2.1. Participants

Data were acquired from a group of 14 patients with mild AD (7 women; mean age 78 ± 4 years) and their relatives (8 husbands/spouses and 6 children), and a group of 17 right-handed elderly control (EC) subjects (13 women; mean age 67 ± 4 years, significantly different from mean age of the AD group, $p < 0.001$) and their relatives (10 husbands/spouses, 4 children, 3 friends). We also included data from a group of 17 young control (YC) subjects (11 women; mean age 23 ± 3 years) and their friends (D'Argembeau et al., 2007), to reveal the full brain network activated by the experimental task in young healthy subjects and to show that changes in AD do not simply correspond to an accentuation of the ageing process. Patients with a diagnosis of probable AD were recruited in the Memory Clinic of the University Hospital in Liège. They all fulfilled international clinical criteria (McKhann et al., 1984). The diagnosis was based on a clinical interview with the patient and a caregiver, and on neurological and neuropsychological examinations. For exclusion criteria, clinical history, general medical examination, laboratory results and structural neuroimaging had been taken into account. Main exclusion criteria were mental retardation, less than 4 years of education, brain trauma, brain lesion (mild degree of leukoaraiosis was accepted), epilepsy, cancer, depression, any major systemic disease or any substance abuse. All patients had impaired episodic memory, as assessed by the free and cued selective reminding test (Grober et al., 1988) and the California verbal learning test (Delis et al., 1987), but the standard (3 h) neuropsychological assessment in the Memory Clinic did not include tests for autobiographical memory nor data on recollection versus familiarity processes during memory retrieval. AD patients were in a mild stage of the disease, with a clinical dementia rating score of 1 at inclusion (Hughes et al., 1982) and they all received an acetylcholinesterase inhibitor. They did not have contraindications for MRI and they were able to read capital letters of a newspaper at a distance of 50 cm without spectacles. Elderly subjects were recruited via poster announcement in a third age club in Liège. All patients and elderly controls were assessed with the dementia rating scale (Mattis, 1976) after the fMRI session and the performance was significantly lower (t-test with $p < 0.001$) in AD patients (mean score 124 ± 5, range 113–135) than in EC (mean score 142 ± 1, range 139–144). Young participants were recruited among the students of the University of Liège. None of the participants in the control groups had any relevant medical history or used any centrally acting medication. Control subjects were paid for their participation. All participants and their representative gave written informed consent prior to their inclusion in the study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège and was performed in accordance with the ethical standards described in the Helsinki declaration.

2.2. Task description

Patients and control subjects participated in the study with someone they personally knew well (a close relative or friend). All subjects were asked to make personality assessments concerning themselves or their relative, taking either their own or their relative's perspective. Hence, the perspective taken by the participants (first- or third-person perspective) and the target person (self or other) were manipulated according to a 2 × 2 factorial design, resulting in four conditions: taking a first-person perspective when judging self-personality (1P_Self), taking a first-person perspective when judging relative's personality (1P_Other), taking a third-person perspective when judging self-personality (3P_Self) and taking a third-person perspective when judging relative's personality (3P_Other).

For a didactic purpose in the description of the task, let us call the subject tested "Nicolas" and his relative "Caroline", so that in the example, the questions are addressed to Nicolas. The 1P_Self condition required Nicolas to evaluate the extent to which the adjectives described his own personality (e.g., "Are you sociable?"), whereas the 1P_Other condition required Nicolas to evaluate the extent to which the adjectives described the personality of Caroline (e.g., "Is Caroline sociable?"). Both these conditions therefore required participants to express their own opinion when making their judgments. By contrast, in the 3P_Self and 3P_Other conditions, participants were asked to take a third-person perspective, i.e. to "put themselves in the shoes of their relative" in order to estimate how the relative would assess his/her own and the participant's personality. Specifically, the 3P_Self condition required Nicolas to evaluate how Caroline perceives his personality (e.g., "According to Caroline, are you sociable?"). In the 3P_Other condition, Nicolas evaluated how Caroline perceives her own personality (e.g., "According to Caroline, is Caroline sociable?").

The same set of 40 trait adjectives was used in all four conditions. These adjectives were selected from those used in previous studies of self-referential personality judgments (Klein et al., 1996) and were translated into French (*poli*, *énergique*, *brillant*, *raffiné*, *timide*, *élégant*, *tolérant*, *honnête*, *irresponsable*, *sociable*, *ennuyeux*, *dévoué*, *aimable*, *logique*, *audacieux*, *agressif*, *ambitieux*, *ingrat*, *bavard*, *drôle*, *imaginatif*, *impatient*, *sensible*, *entêté*, *triste*, *affectueux*, *observateur*, *modeste*, *sympathique*, *attentionné*, *sincère*, *séduisant*, *faible*, *assuré*, *organisé*, *curieux*, *réfléchi*, *égoïste*, *doux*, *économe*). The four conditions were presented in a single session, using a block design. There were 10 blocks per condition. Each block consisted of four trials lasting 5 s each; thus, each block lasted 20 s. In each trial, an adjective was presented for 5 s, during which the participants were required to make their judgment, by pressing one of four buttons (1 = not at all, 2 = a little, 3 = quite well, 4 = completely). The instruction appeared on the screen 3 s before the start of each block, to inform participants about the type of judgment they had to make for the adjectives presented subsequently (1P_Self: "You are"; 1P_Other: "X is"; 3P_Self: "According to X, you are"; 3P_Other: "According to X, s/he is," where "X" was replaced by the first name of the selected friend or relative); then, the four adjectives were presented sequentially below this instruction, which remained on the screen for the entire duration of the block. The four possible answers were displayed below the adjective and remained on the screen also for the entire duration of the block. Blocks were separated by a variable interval of 7–12 s, during which participants passively viewed a fixation cross that was used as a baseline. Four different orders for the presentation of the conditions was generated (A = 1P_Other, 1P_Self, 3P_Other, 3P_Self; B = 1P_Self, 1P_Other, 3P_Self, 3P_Other; C = 3P_Other, 1P_Other, 3P_Self, 1P_Self; D = 3P_Self, 1P_Other, 3P_Other, 1P_Self), and this order was repeated 10 times throughout the scanning session. Each order of condition presentation was equally represented in each group of subjects and the order of adjectives presentation within each condition was randomly modified between subjects of a group. Between subjects partial randomization and random effect analysis of data allowed to avoid any sequential influence of one condition on an other.

Participants performed the judgment tasks either while in the fMRI scanner or out of the scanner. In the YC group subjects and relatives performed the tasks in the fMRI scanner. In the EC group all subjects and three relatives performed the tasks in the scanner and in the AD group none of the relatives provided their judgment in the scanner. The procedure was exactly the same for the relatives who answered out of the scanner and for the fMRI participants. The relatives were installed alone in a quiet room, and a laptop displayed the questions via the matlab code used in the fMRI scanner (so that even the delays between conditions were matched for "behavioral" and "fMRI" participants). They indicated their answers pushing one of four dedicated keys of the keyboard. The order of conditions presentation and of adjectives within each condition was the same for any dyad subject–relative. Most relatives answered the questionnaire by their own, except for some elderly relatives, with impaired finger mobility. In that case, one experimenter stayed in the room and pushed the keys according to the oral answer of the person. Practice trials were performed before the scanning/behavioral session in order to familiarize participants with the four types of judgments.

2.3. Analysis of the behavioral results

For each scanned subject several congruency scores were calculated to assess agreement between subjects and their relative. Such a methodology (comparing self and other on various judgments to highlight abilities and inabilities in self and social knowledge) was introduced into mainstream psychological literature by Klein and colleagues, who widely used it to assess knowledge of self in control populations and demonstrated that the methodology is adequate in patients (Klein et al., 2003, 1996, 2002). Congruency scores revealed the percentage of matching answers, out of 40, between the subject and his/her relative. To decrease the importance of judgment nuances in the scores, we reduced the number of possible answers to two, combining "not at all" and "a little" as negative answers and "quite well" and "completely" as positive answers. The congruency scores presented below were compared between groups with a non parametric Mann–Whitney test.

2.3.1. Third-person perspective congruency score

A third-person perspective congruency score when the target person is the relative measured the level of congruency between answers of the subject in 3P_Other condition (Nicolas is asked "According to Caroline, is Caroline sociable?") and answers of the relative in 1P_Self (Caroline is asked "Are you sociable?"). A third-person perspective congruency score when the target person is the self measured the level of congruency between answers of the subject in 3P_Self condition (Nicolas is asked "According to Caroline, are you sociable?") and answers of the relative in 1P_Other (Caroline is asked "Is

Please cite this article in press as: Ruby, P., et al., Perspective taking to assess self-personality: What's modified in Alzheimer's disease?, Neurobiol Aging (2008), doi:10.1016/j.neurobiolaging.2007.12.014

Nicolas sociable?”). In order to have a global measure of the third-person perspective ability of the subjects, the mean of 3P congruency score on other and 3P congruency score on self was computed.

2.3.2. *Personality awareness score*

“Self” personality awareness score measured the awareness that the subject had of his own personality using the report of the relative as reference. It contrasted the answers of the subject in 1P_Self (Nicolas is asked “Are you sociable?”) with the answers of the relative in 1P_Other (Caroline is asked “Is Nicolas sociable?”). “Other” personality awareness score measured the awareness that the subject had of the personality of his/her relative. It contrasted the answers of the subject in 1P_Other (Nicolas is asked “Is Caroline sociable?”) with the answers of the relative in 1P_Self (Caroline is asked “Are you sociable?”). In order to have a global measure of the personality awareness of the subjects, the mean of “self” and “other” personality awareness scores was computed.

2.3.3. *Self-judgment “accuracy” score (irrespective of the perspective taken)*

A mean of the third-person perspective congruency score on self and the self-personality awareness score was used as a global score assessing self-judgment accuracy (irrespective of the perspective taken).

2.4. *MRI acquisition*

Data were acquired on a 3 T scanner (Siemens, Allegra, Erlangen, Germany) using a T2* sensitive gradient echo EPI sequence (TR = 2130 ms, TE = 40 ms, FA 90°, matrix size 64 × 64 × 32, voxel size 3.4 mm × 3.4 mm × 3.4 mm). Thirty-two 3-mm thick transverse slices (FOV 22 cm × 22 cm) were acquired, with a distance factor of 30%, covering the whole brain. Structural images were obtained using a T1-weighted 3D MP-RAGE sequence (TR = 1960 ms, TE = 4.4 ms, FOV 23 cm × 23 cm, matrix size 256 × 256 × 176, voxel size 0.9 mm × 0.9 mm × 0.9 mm). In each session, between 629 and 650 functional volumes were obtained. The first three volumes were discarded to account for T1 saturation. Head movement was minimized by restraining the subject’s head using a vacuum cushion. Stimuli were displayed on a screen positioned at the rear of the scanner, which the subject could comfortably see through a mirror mounted on the standard head coil.

2.5. *MRI analyses*

Data were preprocessed and analyzed using SPM2 software (Wellcome Department of Imaging Neuroscience, http//www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks Inc., Sherborn, MA). Functional scans were realigned using iterative rigid body transformations that minimize the residual sum of squares between the first and subsequent images. They were normalized to the MNI EPI template (voxel size: 2 mm × 2 mm × 2 mm) and spatially smoothed with a Gaussian kernel with full-width at half maximum (FWHM) of 8 mm.

For each participant, brain responses were estimated at each voxel, using a general linear model with block regressors. Block regressors looked for brain activity separately for the 1P_Self, 1P_Other, 3P_Self and 3P_Other conditions. For each condition, blocks pertained to the period from the appearance of the first adjective to the disappearance of the last adjective; therefore, the duration of each block was 20 s. Boxcar functions representative of these block conditions were convolved with the canonical hemodynamic response. The design matrix also included the realignment parameters to account for any residual movement-related effect. A high pass filter was implemented using a cut-off period of 128 s in order to remove the low-frequency drifts from the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order 1 (+ white noise). The contrasts of interest were the main effect of self as judgment target [self vs. other: (1P_Self + 3P_Self)–(1P_Other + 3P_Other)]; the main effect of judgment from a third-person perspective [third-person vs. first-person: (3P_Self + 3P_Other)–(1P_Self + 1P_Other)]; the specific effect of third-person perspective on self [(3P_Self–3P_Other)–(1P_Self–1P_Other)]. The resulting set of voxel values constituted a map of t statistics [SPM{T}]. The contrast images were further smoothed (6-mm FWHM Gaussian kernel) to accommodate to interindividual variability in brain anatomy. Contrasts were then entered in a second-level analysis, corresponding to an ANOVA model to look for the effect within and between groups, controlling for non-sphericity of the variances. One-sample and two-sample t-tests assessed the significance of the effects within and between groups respectively. Since age differed between AD patients and elderly controls, we checked that its introduction as a confounding covariate did not modify the results. The results of the two-sample t tests EC > AD and AD > EC (and YC > EC for completeness) were masked by the effect in the EC, AD and YC group respectively. For example, masking EC > AD by EC enabled us to consider differences only in the brain regions where an activation was detected in EC. The resulting SPM{T} maps were thresholded at $P < .001$. As a rule, statistical inferences were performed with a small volume correction at the voxel level ($P < .05$). The small volume was defined as a10-mm radius sphere around a published coordinates in a brain area predicted to be involved in a given contrast.

Finally, correlations between “congruency scores” and brain activation were searched for, but we did not obtain any significant result (probably due to our small samples).

2.6. *A priori locations of interest*

Predictions were made according to previous reports on personality traits assessments, perspective taking, autobiographical memory and familiarity-based (noetic) versus recollective (autonoetic) retrieval. As a consequence, regions of interest for data analysis were selected on the basis of the activations foci reported in these studies. All stereotactic coordinates refer to the MNI space (published coordinates that referred to the atlas space of Talairach and Tournoux were transformed to the MNI space). The *a priori* locations of interest (x, y, z) for self-referential processing were the following: (2, 54, 4) in the ventromedial prefrontal cortex (D'Argembeau et al., 2005; Johnson et al., 2002; Kelley et al., 2002; Schmitz et al., 2004); (6, 34, 4) in the anterior cingulate cortex (Craik, 1999); (−4, 18, −10) in the subgenual cortex (Schmitz et al., 2004); (−16, 40, 32 and 10, 50, 20) in the dorsomedial prefrontal (Fossati et al., 2003); (−12, 40,42) in the superior frontal sulcus (Ochsner et al., 2005); (−26, −51, 50) in the intraparietal sulcus (IPS) (Kircher et al., 2000); (2, −60, 16) in the precuneus (Schmitz et al., 2004). Concerning familiarity and recollection-based processes, we respectively selected (−30, −60, 36 and 39, −51, 36) in the intraparietal sulcus (Henson et al., 1999; Maril et al., 2003; Yonelinas et al., 2005); (−52, −48, 40) in the inferior parietal (Henson et al., 1999). For recollection of autobiographical events, we also selected (−14, −10, −16) in the hippocampus (Viard et al., 2007). Concerning perspective-taking, we selected (−4, 12, 66) in the dorsomedial prefrontal cortex (Ruby and Decety, 2001, 2003); (50, −58, 30 and −58, −58, 28) in the inferior parietal lobe (Ruby and Decety, 2001, 2004); (−10, −62, 38) in the precuneus (Ruby and Decety, 2001); (−57, 26, 19) in the inferior frontal gyrus (Vogeley et al., 2001); (−30, −3, 56) in the middle frontal gyrus (Vogeley et al., 2004); (−24, 50, −6) in the lateral orbitofrontal cortex (Rubia et al., 2003); (2, −80, 6 and −20, −88, −6) in the lingual gyrus (Ochsner et al., 2005, 2004). Note that most regions would belong to a core brain network subserving diverse forms of self-projection, such as self-evaluation and conceiving the viewpoint of others (Buckner and Carroll, 2007).

3. Results

3.1. Behavioral results

For the third-person perspective congruency score (subject's third-person assessment compared to the relative's judgment, concerning the subject and the relative), Mann–Whitney test revealed no significant difference ($p = .30$) between the two control groups (YC: median score = 53%, min = 45%, max = 65%; EC: median score = 51%, min = 37%, max = 65%) and a significant difference between the AD group (median score = 44%, min = 31%, max = 57%) and the elderly control group (median (EC) score > median(AD) score, $p = .03$; see Fig. 1).

For the personality awareness score (subject's first-person assessment compared to the relative's assessment, irrespective of the target), Mann–Whitney test revealed no significant difference between groups (AD: median score = 46%, min = 27%, max = 62%; EC: median score = 51%, min = 39%, max = 57%; YC: median score = 49%, min = 40%, max = 57%). This result showed that AD patients were able to perform the task, without more first-person perspective errors than elderly controls. Note that the self-personality awareness score alone was not significantly lower in AD patients than in elderly controls (AD: median score = 44%; min = 22%; max = 57%; EC: median score = 50%; min = 25%; max = 60%, $p > .05$).

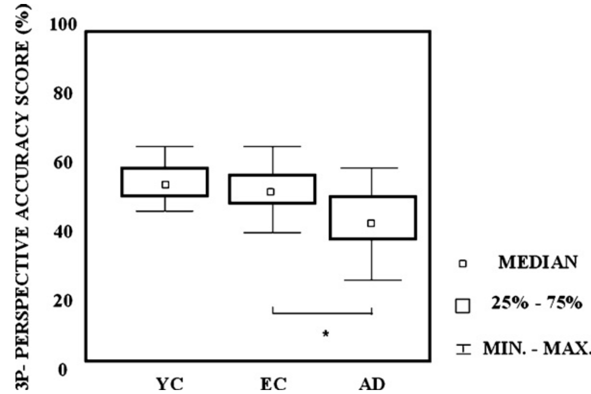

Fig. 1. Median of third-person perspective accuracy score, revealing the percentage of correct prediction of the relative's answers, in young (YC) and elderly healthy controls (EC) and Alzheimer patients (AD). *$p < .05$. In the AD group the subject–relative congruency is significantly lower than in the elderly control group suggesting that AD patients make more mistakes in relatives' answers prediction than elderly control subjects.

For the self-judgment "accuracy" score (subject's assessment of self, compared to the relative's judgment, irrespective of the perspective taken), Mann–Whitney test revealed no significant difference ($p = .44$) between the two control groups (YC: median score = 52%, min = 36%, max = 61%; EC: median score = 49%, min = 37%, max = 65%) and a significant difference between the AD group (median score = 44%; min = 27%; max = 56%) and the elderly control groups (median (EC) score > median (AD) score, $p = .04$).

3.2. fMRI results

3.2.1. Main effect of the target person: self versus other (see Fig. 2)

3.2.1.1. Young healthy controls. Data on young volunteers are reported in detail elsewhere (Fig. 2, D'Argembeau et al., 2007) but they were included (1) to show the global cerebral network activated by the task and (2) to demonstrate that differences between AD and EC were not due to an accelerated ageing effect. When the target person of the personality judgement was the self as opposed to the relative, irrespective of the perspective used to judge [(1P_Self + 3P_Self)–(1P_Other + 3P_Other)], a large activation cluster was observed in the medial prefrontal cortex (MPFC), which encompassed the dorsal and ventral portions of the medial prefrontal cortex and the anterior cingulate cortex. This contrast also yielded significant activation in the

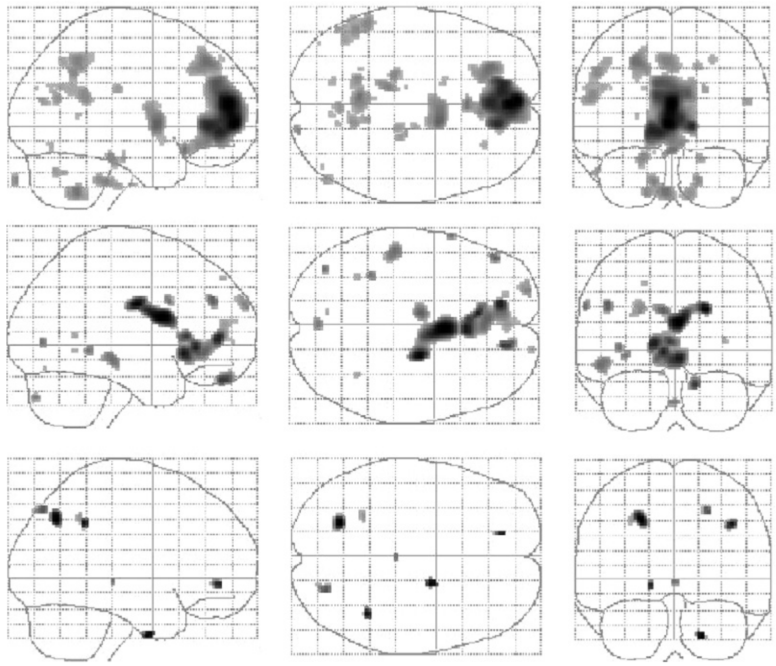

Fig. 2. "Glass brain" presentation of activation during self (vs. other) assessment of adjectives in the three groups. SPM are displayed at $p < .001$.

superior frontal sulcus, the precuneus and the inferior parietal lobe (see Table 1 and D'Argembeau et al., 2007).

3.2.1.2. Elderly healthy controls. In this group the main effect of self versus other resulted in significant effects in the ventromedial and the anterior dorsomedial prefrontal cortex (see Table 1).

3.2.1.3. Alzheimer patients. When AD patients assessed their own (vs. their relative's) personality whatever the perspective, significant activations were detected in the intraparietal sulcus in both hemispheres (see Table 1).

3.2.1.4. Between groups comparisons. In comparison to EC, YC showed significantly more activation in the dorsomedial prefrontal cortex (DMPFC) and in the precuneus, while AD patients had more activation in the intraparietal sulcus (see Table 1 and Fig. 3) than EC. The DMPFC was more activated in EC than in AD patients.

3.2.2. Main effect of perspective taking: third-person versus first-person (see Fig. 4)

3.2.2.1. Young healthy controls. When subjects took their relative's perspective versus their own, irrespective of the target person [(3P_Self + 3P_Other)–(1P_Self + 1P_Other)],

Table 1
Main effect of the target person, self vs. other [(1P_Self + 3P_Self)–(1P_Other + 3P_Other)]

Brain regions	Young controls				Elderly controls				AD patients			
	x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*
VMPFC	−2	52	12	(5.53)	−6	50	8	(3.36)				
ACC	0	38	0	(4.85)	0	34	−4	(3.47)				
Subgenual cortex					4	22	−6	(4.16)				
DMPFC	−8	44	28	(4.17)[a]	−8	42	30	(3.26)[b]				
	2	52	16	(5.40)								
SF sulcus	−22	40	42	(3.80)								
Precuneus	2	−68	22	(3.41)[a]								
IP sulcus									−22	−66	40	(3.48)[a]
									−26	−50	42	(3.170[a]
									40	−48	38	(3.53)
IPL	−52	−54	36	(3.47)								

Significant threshold $P < .05$ after correction for multiple comparisons (see Section 2 for details on small volume correction). VMPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex; DMPFC = dorsomedial prefrontal cortex; SF = superior frontal; IP = intraparietal; IPL = inferior parietal lobule; *x*, *y* and *z* in MNI space (*x* negative is left sided).
[a] Significantly more activated than in elderly controls.
[b] More activated in elderly controls than in AD patients.

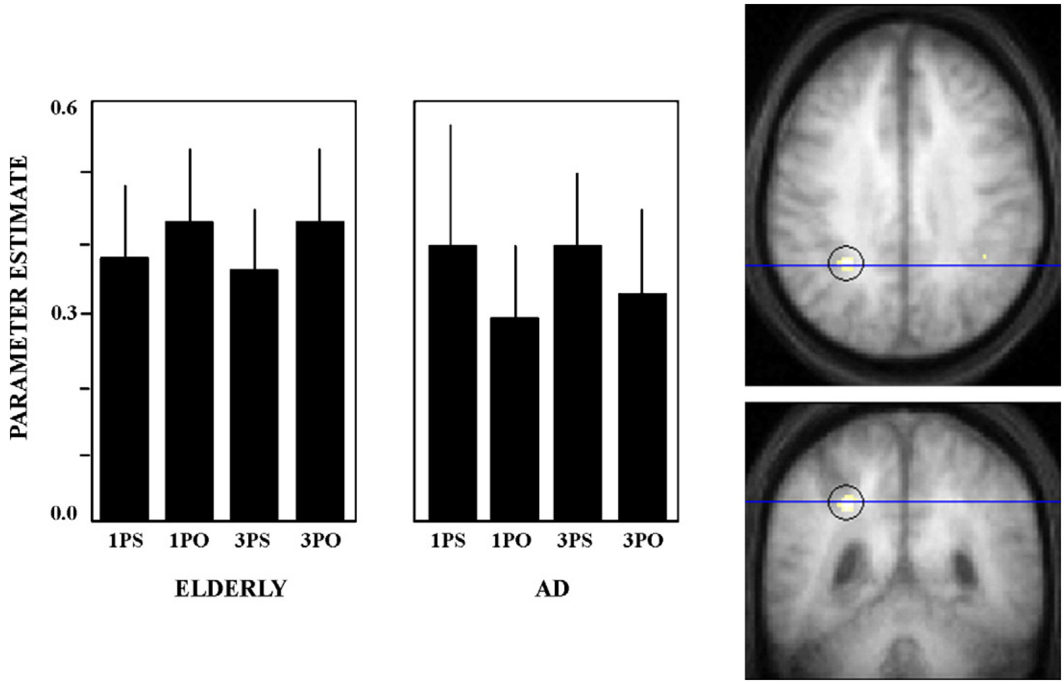

Fig. 3. Transverse and coronal sections of the brain showing a cluster in the intraparietal sulcus which is significantly more activated in the AD group than in the EC group for the main effect "self vs. other". The focus of activation is displayed at $p < .001$ on the mean MRI structural image of the AD patients. 1PS = first-person perspective on self; 1Po = first-person perspective on other; 3Ps = third-person perspective on self; 3Po = third-person perspective on other. Mean parameter estimates are presented with standard deviation.

significant prefrontal activations were detected in the left posterior DMPFC. This contrast also yielded activation in the inferior parietal lobe, in the precuneus and in the lingual gyrus (Fig. 4) (see Table 2 and D'Argembeau et al., 2007).

3.2.2.2. Elderly healthy controls. In this group the main effect of third- versus first- person perspective resulted in significant activation in the lingual gyrus bilaterally (see Table 2).

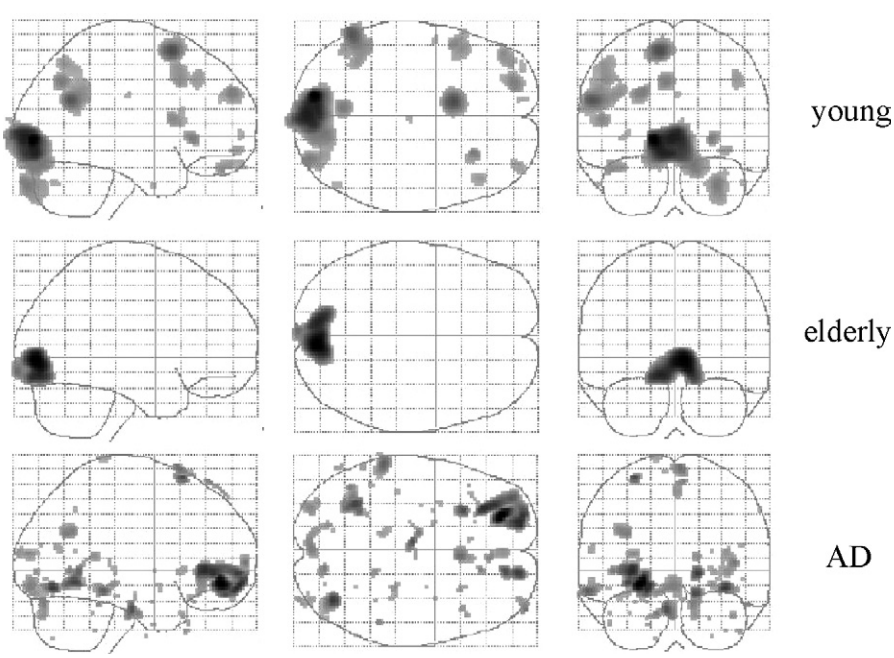

Fig. 4. "Glass brain" presentation of activation during third (vs. first) person perspective taking in the three groups. SPM displayed at $p < .001$.

Please cite this article in press as: Ruby, P., et al., Perspective taking to assess self-personality: What's modified in Alzheimer's disease?, Neurobiol Aging (2008), doi:10.1016/j.neurobiolaging.2007.12.014

Table 2
Main effect of perspective taking, third-person vs. first-person [(3P_Self + 3P_Other)–(1P_Self + 1P_Other)]

Brain regions	Young controls				Elderly controls				AD patients			
	x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*
Lingual gyrus	−14	−86	−2	(6.61)[a]	8	−84	−4	(5.83)				
	2	−88	0	(5.56)	−6	−82	−10	(5.46)				
IPL	−62	−60	26	(3.98)								
Precuneus	−4	−66	40	(3.17)								
DMPFC	−10	14	60	(3.88)[a]					4	18	72	(3.54)[a]
OFC									−24	46	−8	(4.55)[a]

Significant threshold $P < .05$ after correction for multiple comparisons (see Section 2 for details on small volume correction). IPL = inferior parietal lobule; DMPFC = dorsomedial prefrontal cortex; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; OFC = orbitofrontal cortex; *x*, *y* and *z* in MNI space (*x* negative is left sided).

[a] Significantly more activated than in elderly controls (the inverse contrasts did not show any significant result).

3.2.2.3. Alzheimer patients. When AD patients tried to put themselves in the shoes of their relative (vs. taking a first-person perspective) whatever the target person judged, significant activations were detected in the posterior part of the DMPFC and in the lateral orbitofrontal cortex (see Table 2).

3.2.2.4. Between groups comparisons. In comparison to EC, YC showed significantly more activation in the lingual gyrus and in the posterior part of the DMPFC, while AD patients, by comparison to EC, had more activation in the posterior part of the DMPFC and in the orbitofrontal cortex (see Table 2 and Fig. 5). No regions were found to be significantly more activated in EC than in YC or AD.

3.2.3. Interaction between perspective taking and target person

A trend in DMPFC activation was observed in young controls, this region being the more activated when the subject took a third-person perspective on the self-personality (D'Argembeau et al., 2007). No significant result was detected for the interaction contrast in the EC and AD group, so that interaction will not be further discussed in this report.

4. Discussion

In this fMRI study, we investigated the cerebral correlates of self-processing and perspective taking abilities in

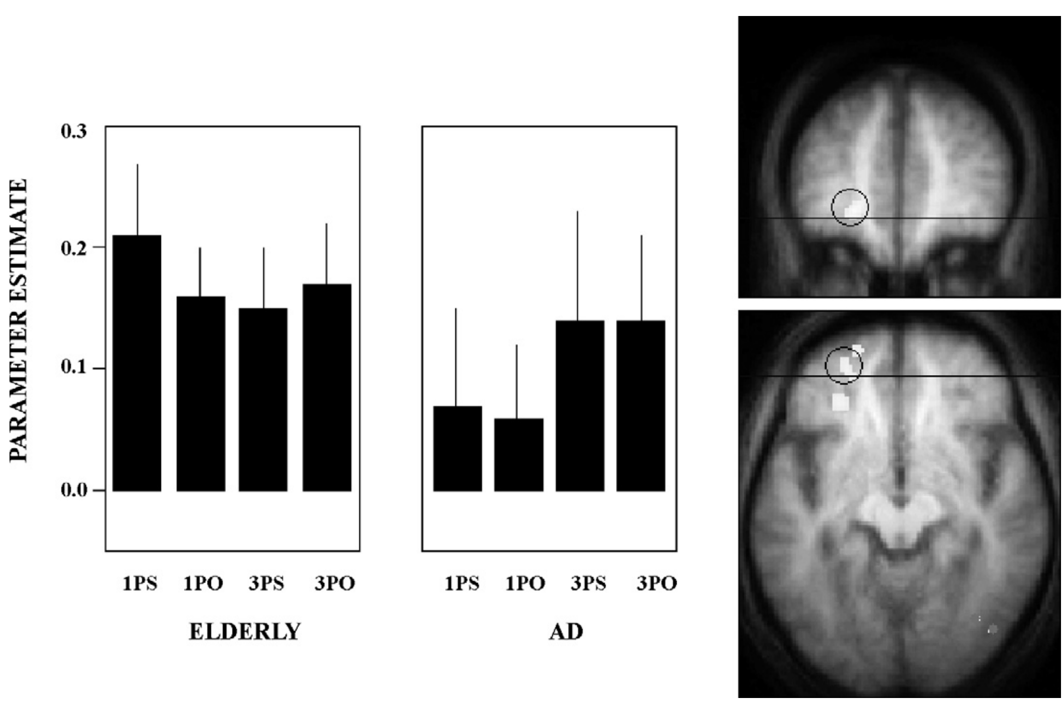

Fig. 5. Transverse and coronal sections of the brain showing a cluster in the orbitofrontal cortex which is significantly more activated in the AD group than in the EC group for the main effect "third- vs. first-person perspective". The focus of activation is displayed at $p < .001$ on the mean MRI structural image of our AD patients. Mean parameter estimates are presented with standard deviation.

Please cite this article in press as: Ruby, P., et al., Perspective taking to assess self-personality: What's modified in Alzheimer's disease?, Neurobiol Aging (2008), doi:10.1016/j.neurobiolaging.2007.12.014

AD patients using a paradigm of personality assessment. We used congruency scores between responses of patients and relatives to assess behavioral "performance". Patients did not demonstrate significant decrease in global (i.e. own and relative's) personality awareness (demonstrating that they were as good as controls at performing the task), but they were impaired in third-person perspective taking (irrespective of the target, i.e. self or relative) and in self-judgment "accuracy" (irrespective of the perspective, i.e. first- or third-person perspective on self). These behavioral results were paralleled by functional cerebral modifications in AD patients. For self (vs. other) personality judgment, AD patients relied more than healthy controls on the intraparietal sulcus. In addition, when they took the perspective of their relative (vs. their own), AD patients recruited the posterior dorsomedial prefrontal cortex and the orbitofrontal cortex to a greater extent than elderly controls (but similarly to young volunteers). The comparisons between young and elderly healthy subjects demonstrated that the regional differences between AD and elderly controls did not simply correspond to an accentuation of the differences already observed in normal aging.

This study thus evidences behavioral and neurophysiological differences between AD and healthy elderly subjects, for self-personality assessment and third-person perspective taking. These results will be interpreted according to the literature on the cerebral correlates of memory and evaluative reasoning in healthy subjects. In order to clarify the discussion, the subject will be named Nicolas and his relative Caroline in the following paragraphs (see Section 1).

4.1. The impact of aging on the task

No significant differences in behavioral performance were found between young and elderly groups, and both groups recruited ventromedial prefrontal regions for self-assessment (Gutchess et al., 2007). However, some differences in brain activations were found between these two groups for both self (vs. other) personality judgement and third-person (vs. first-person) perspective taking. Such modified brain activity subserving similar performance may reveal different but equally efficient strategies to resolve the tasks in the young and the elderly subjects. Anterior DMPFC and precuneus were more activated in YC than in EC for self (vs. other) personality assessment. The regions are known to be involved in reflection processing (such as inductive reasoning) and memory retrieval respectively (Cavanna and Trimble, 2006; D'Argembeau et al., 2005; Goel et al., 1997; Ries et al., 2006). For third-person perspective taking, YC activated more the lingual gyrus and the posterior DMPFC than elderly subjects. These regions could be respectively associated with a more vivid visual imagery in relation to episodic memory retrieval during the task (Greenberg and Rubin, 2003) and with inferring mental state of others (Calarge et al., 2003; Mitchell et al., 2004). Overall, these findings suggest that young students may rely more on episodic memory retrieval and inferring than elderly subjects to perform the task. In young subjects, representations of their own and their relative's personality might not be as well established as in older adults that have spend many years of common life. Due to their well established knowledge of their relative's personality and their confidence in this knowledge, elderly controls would recruit less reasoning processes than young subjects to answer the questions. A further explanation is that recollective processes are more readily available in young than in elderly volunteers (Bastin and Van der Linden, 2003; Hay and Jacoby, 1999; Parkin and Walter, 1992; Prull et al., 2006).

4.2. Self-personality representation in AD

Although self-awareness scores (assessed as congruency between patient and relative assessment about patient's personality, i.e. Nicolas's versus Caroline's first-person perspective on Nicolas' personality) were somewhat lower in the AD group than in controls, this decrease did not reach significance. Previous reports showed a global preservation of self-personality awareness in AD patients, but unequal level of assessment accuracy depending on the facet of personality tested (Rankin et al., 2005). As we tested many facets of the self when presenting 40 different personality trait adjectives, mixed congruent (i.e. "accurate") and divergent (i.e. "inaccurate") answers between AD patients and their relatives might explain lack of significantly decreased score in the AD group. However, it cannot be concluded from this lack of discrepancy between patient's and relative's (first-person perspective) assessment about patient's personality that awareness of self-personality is not impaired in AD patients. Indeed, the self-judgment "accuracy" score (mean of patient's first- and third-person perspective about the self compared to relative's assessment about patient's personality) showed that AD patients assessed their own personality less accurately than healthy subjects.

This diminution of self-judgment "accuracy" was associated with modifications of brain activation in mild stage AD patients in comparison to healthy subjects. When assessing self (vs. other) relevance of personality traits adjectives (irrespective of the perspective taken), AD patients mainly activated intraparietal areas while elderly volunteers essentially recruited VMPFC (Table 1). The main activation found in EC is in agreement with previous results of neuroimaging studies investigating self-processing in young healthy subjects. The VMPFC was indeed frequently involved in self-personality assessment in groups of young volunteers (D'Argembeau et al., 2005; Kelley et al., 2002) and this region was also detected during personal events recollection (Svoboda et al., 2006; Yonelinas et al., 2005) and evaluative reasoning (Christoff et al., 2001; Goel et al., 1995; Ruby and Legrand, 2008; Zysset et al., 2002). In our AD patients, assessment of self-relevance was accompanied by bilateral activation around the intraparietal sulcus. Due to their characteristic episodic memory impairments (Piolino et al., 2003), we hypothesized that AD patients would rely on semantic more than on episodic personal (and general) information to provide judgment on self-personality. Our results fit well with this prediction since the intraparietal sulci was previously involved in self-processing (Kircher et al., 2000; Ochsner et al., 2005) and was activated for familiarity-based judgments during recognition tasks (Klein et al., 2003; Wagner et al., 2005). This hypothesis also fits with the finding that the anterior DMPFC was more activated in elderly controls than in AD patients, suggesting that elderly controls used more reflective, recollective and evaluative processes than AD subjects to perform the task (D'Argembeau et al., 2005; Dobbins et al., 2003; Zysset et al., 2002). In summary, we suggest that IPS activation during self-personality assessment in AD is associated with familiarity-based retrieval of old personal semantic information.

4.3. Third-person perspective taking in AD

Third-person perspective congruency scores (Nicolas's third-person vs. Caroline's first-person perspective on Caroline's personality) were lower in the AD patients group than in elderly controls. This result is consistent with previously reported impairment of theory of mind in AD (Gregory et al., 2002) and confirms a deficit in other's mind representation in these patients even in the early stage of the disease. Perspective taking is a constructive process of inferring (Wilson and Dunn, 2004) that recruits prefrontal regions (D'Argembeau et al., 2007), and we anticipated that impaired mentalizing in AD would modify their frontal activation during the task. We could imagine either decrease or increase of activation compared to controls, as previously reported in memory tasks (Backman et al., 1999; Becker et al., 1996; Prvulovic et al., 2005). When AD patients took the perspective of their relative (vs. their own), they recruited more than elderly controls the posterior DMPFC and the lateral orbitofrontal cortex. The posterior DMPFC was repeatedly involved in inferring the mental states of others (Calarge et al., 2003; Mitchell et al., 2004; Ruby and Decety, 2004) and in top–down monitoring (Levine et al., 2004). The lateral orbitofrontal cortex was shown to be activated when subjects were engaged in tasks requiring executive processing such as reasoning (Goel et al., 1997) and when they took a "cognitive" third-person perspective (Hynes et al., 2006). Our proposal to explain the preferential recruitment of prefrontal regions in AD patients compared to elderly controls during third-person perspective taking is the following: a solid and reliable knowledge of self and relative's personality (thanks to many years of common life during which personality remained stable) might explain a diminished need in inferring and reasoning to predict the relative's answers in the EC group. When taking a third-person perspective, elderly volunteers would essentially rely on well established representations of their relative, that can be (partly) stored in ventral occipital areas (Ranganath et al., 2004). Congruently, the lingual gyrus is known to be involved in autobiographical memory retrieval, particularly for visual imagery components (Conway et al., 2002; Greenberg and Rubin, 2003). In contrast, AD patients, who suffer from memory impairment, may rely on inferring and monitoring to answer third-person perspective questions. According to our results, recruitment of frontal cortices in mild AD patients would not be efficient to counterbalance memory loss in all cases (because perspective taking is based on false premises or because the cerebral network subserving perspective taking is impaired), and patient would not be able to prevent from making errors in third-person perspective taking on self (and other) personality. AD patients seem to rely on familiarity-based judgments and non-updated (distorted) semantic representations, especially for the self (Klein et al., 2003). Such inability to adequately select low-weight recent memories (such as recent complaints of the relative about personality changes) more than past (non-updated) memories on self-personality may be one of the reasons why perspective taking, based on false premises, fails in AD patients. Such interpretation is congruent with a recent study (Mimura and Yano, 2006) that showed that AD patients, even if able to consider feedbacks online and modify their judgment accordingly, failed to subsequently incorporate incidents of memory failure into generalized self-belief systems.

4.4. How to explain anosognosia?

The patients included in this study had early memory impairment, however we know from the literature that memory deficits are not sufficient to explain anosognosia (Agnew and Morris, 1998). Our hypothesis is that perspective taking deficits may participate in the inability of demented patients to adequately process a mismatch between self and other perspective on self abilities (Salmon et al., 2005b). We propose that, when an AD patient assesses his own personality (recruiting familiarity-based processes and IPS) in a way that contradicts his current behavior, only others' reaction can tell him that he is wrong. If the patient cannot correctly represent others' reaction and mind, he may have little cue that there is a mismatch. We know from the literature that when early AD patients are explicitly told by the experimenter that there is a mismatch, they may process it and correct their self-representation accordingly. However such correction lasts for a short period and is soon forgotten (Mimura and Yano, 2006). Hence as they cannot rely on episodic memory, patients may critically need the online representation of other's mind about themselves to identify a mismatch and to correct the self-representation accordingly. Interestingly third-person perspective deficits may explain why patients lack awareness selectively for some type of personality trait (Rankin et al., 2005). Personality traits for which AD patients lack self-awareness involve social emotions: patients significantly underestimated the degree to which they exhibited unassured and submissive behaviors, and overestimated their degree of extraversion (Rankin et al., 2005; Robert et al., 2002). Since social emotion requires a third-person perspective on the self, i.e. the representation of the opinion of the other on the self (Takahashi et al., 2004), assessment of personality trait referring to social emotion (such as *boring*,

Please cite this article in press as: Ruby, P., et al., Perspective taking to assess self-personality: What's modified in Alzheimer's disease?, Neurobiol Aging (2008), doi:10.1016/j.neurobiolaging.2007.12.014

ungrateful, *affectionate, selfish*, *polite* in our experiment) might be particularly hampered by third-person perspective taking deficits in AD.

4.5. Methodological considerations and alternative explanations?

In our AD population, hemodynamic and metabolic abnormalities related to the neurodegenerative process could affect the fMRI hemodynamic response. This is rarely addressed in the literature, but a *positive* correlation was reported between left inferior frontal activation during a semantic task and local atrophy in AD patients (Johnson et al., 2000). Our structural (magnetic resonance imaging) images were used to localize regional activation, but they were not adequate for measuring atrophy (due to relatively poor grey/white matter distinction), and we could not correct our results for regional loss of grey matter in subregions of the cerebral cortex. Consequently, the main results observed in AD subjects (activation in the fundus of the intraparietal sulci) might be overestimated compared to controls. Moreover, one should be cautious when comparing patients with elderly controls, since the neurovascular coupling may differ between groups, and one cannot exclude an influence of the cholinergic medication in AD patients.

Another way to interpret our results is to consider a non-specific attentional recruitment during the tasks in AD. Indeed, overactivated regions in the patients compared to elderly controls (IPS for self vs. other; dorsomedial and orbitolateral prefrontal cortex for third- vs. first-person perspective) all belong to the attentional networks (Chaminade and Fonlupt, 2003; Majerus et al., 2007) and especially to the goal-directed attention network described by Corbetta and Shulman (2002). We may speculate that patients with mild AD were especially motivated and willing to collaborate in our study, which could explain an important attentional recruitment in AD patients during the task. This interpretation would also fit with results showing prefrontal cortex involvement in the modulation of emotional judgment by cognition in normal healthy subjects (Blair et al., 2007; Schaefer et al., 2003). It is to note however, that if our result are explained by an increased attentional load in AD versus healthy elderly, this “effort” is not sufficient for preventing errors in AD.

4.6. Conclusion

In conclusion, this study demonstrated that early stage AD patients encounter a decrease in self-personality judgment accuracy and perspective taking ability in addition to their memory impairment. For self-processing, patients essentially activated the intraparietal sulcus, a region involved in familiarity-based retrieval of information. The data are in keeping with the idea that AD patients essentially rely on familiarity to provide self-judgment (Klein et al., 2003). Impaired third-person perspective taking was accompanied by an increase in prefrontal activity in AD, interpreted as a recruitment of inferring and monitoring more than memory processes during the task. Anosognosia for changes in self-personality might derive from familiar judgments based on old semantic knowledge in the absence of retrieval of episodic (recently updated) information on self, and from an inability to use third-person perspective for correcting self-evaluation.

Disclosure statement

There is no conflict of interest for any author concerning this manuscript.

Acknowledgments

This work was supported by the National Fund for Scientific Research (FNRS), by the University of Liège, by the InterUniversity Attraction Pole P 6/29 (Belgian State-Belgian Science Policy), by the EC-FP6-project DiMI, LSHB-CT-2005-512146, and by the European Community, which granted P. Ruby a Marie Curie Individual fellowship. AD, EB, FC, and PM are supported by the FNRS.

References

Adam, S., Van der Linden, M., Collette, F., Lemauvais, L., Salmon, E., 2005. Further exploration of controlled and automatic memory processes in early Alzheimer’s disease. Neuropsychology 19 (4), 420–427.

Addis, D.R., Wong, A.T., Schacter, D.L., 2007. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia 45 (7), 1363–1377.

Agnew, S.K., Morris, R.G., 1998. The heterogeneity of anosognosia for memory impairment in Alzheimer’s disease: a review of the literature and a proposed model. Aging Ment. Health 2, 7–19.

Andreasen, N.C., O’Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1995. Remembering the past: two facets of episodic memory explored with positron emission tomography. Am. J. Psychiatry 152 (11), 1576–1585.

Backman, L., Andersson, J.L., Nyberg, L., Winblad, B., Nordberg, A., Almkvist, O., 1999. Brain regions associated with episodic retrieval in normal aging and Alzheimer’s disease. Neurology 52 (9), 1861–1870.

Bastin, C., Van der Linden, M., 2003. The contribution of recollection and familiarity to recognition memory: a study of the effects of test format and aging. Neuropsychology 17 (1), 14–24.

Becker, J.T., Mintun, M.A., Aleva, K., Wiseman, M.B., Nichols, T., Dekosky, S.T., 1996. Alterations in functional neuroanatomical connectivity in Alzheimer’s disease. Positron emission tomography of auditory verbal short-term memory. Ann. NY Acad. Sci. 777, 239–242.

Blair, K.S., Smith, B.W., Mitchell, D.G., Morton, J., Vythilingam, M., Pessoa, L., Fridberg, D., Zametkin, A., Sturman, D., Nelson, E.E., Drevets, W.C., Pine, D.S., Martin, A., Blair, R.J., 2007. Modulation of emotion by cognition and cognition by emotion. Neuroimage 35 (1), 430–440.

Buckner, R.L., Carroll, D.C., 2007. Self-projection and the brain. Trends Cogn. Sci. 11 (2), 49–57.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer’s disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25 (34), 7709–7717.

Calarge, C., Andreasen, N.C., O'Leary, D.S., 2003. Visualizing how one brain understands another: a PET study of theory of mind. Am. J. Psychiatry 160 (11), 1954–1964.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129 (Pt 3), 564–583.

Chaminade, T., Fonlupt, P., 2003. Changes of effective connectivity between the lateral and medial parts of the prefrontal cortex during a visual task. Eur. J. Neurosci. 18 (3), 675–679.

Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J.K., Holyoak, K.J., Gabrieli, J.D., 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage 14 (5), 1136–1149.

Conway, M.A., Pleydell-Pearce, C.W., Whitecross, S., Sharpe, H., 2002. Brain imaging autobiographical memory. Psychol. Learn. Motiv. 41, 229–263.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3 (3), 201–215.

Craik, F., 1999. In search of the self: a positron emission tomography study. Psychol. Sci. 10, 26–34.

Cuerva, A.G., Sabe, L., Kuzis, G., Tiberti, C., Dorrego, F., Starkstein, S.E., 2001. Theory of mind and pragmatic abilities in dementia. Neuropsychiatry Neuropsychol. Behav. Neurol. 14 (3), 153–158.

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 44 (12), 2308–2314.

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., Luxen, A., Salmon, E., 2005. Self-referential reflective activity and its relationship with rest: a PET study. Neuroimage 25 (2), 616–624.

D'Argembeau, A., Ruby, P., Collette, F., Degueldre, C., Balteau, E., Luxen, A., Maquet, P., Salmon, E., 2007. Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective-taking. J. Cogn. Neurosci. 19, 935–944.

Dalla Barba, G., 1997. Recognition memory and recollective experience in Alzheimer's disease. Memory 5 (6), 657–672.

DeBettignies, B.H., Mahurin, R.K., Pirozzolo, F.J., 1990. Insight for impairment in independent living skills in Alzheimer's disease and multi-infarct dementia. J. Clin. Exp. Neuropsychol. 12 (2), 355–363.

Delis, D., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test, Adult Version. The Psychological Corporation, San Antonio.

Derouesne, C., Thibault, S., Lagha-Pierucci, S., Baudouin-Madec, V., Ancri, D., Lacomblez, L., 1999. Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. Int. J. Geriatr. Psychiatry 14 (12), 1019–1030.

Dobbins, I.G., Rice, H.J., Wagner, A.D., Schacter, D.L., 2003. Memory orientation and success: separable neurocognitive components underlying episodic recognition. Neuropsychologia 41 (3), 318–333.

Fabrigoule, C., Rouch, I., Taberly, A., Letenneur, L., Commenges, D., Mazaux, J.M., Orgogozo, J.M., Dartigues, J.F., 1998. Cognitive process in preclinical phase of dementia. Brain 121 (Pt 1), 135–141.

Fossati, P., Hevenor, S.J., Graham, S.J., Grady, C., Keightley, M.L., Craik, F., Mayberg, H., 2003. In search of the emotional self: an FMRI study using positive and negative emotional words. Am. J. Psychiatry 160 (11), 1938–1945.

Frith, U., Frith, C.D., 2003. Development and neurophysiology of mentalizing. Philos. Trans. Roy. Soc. Lond. B: Biol. Sci. 358 (1431), 459–473.

Gambini, O., Barbieri, V., Scarone, S., 2004. Theory of mind in schizophrenia: first person vs. third-person perspective. Conscious Cogn. 13 (1), 39–46.

Gil, R., Arroyo-Anllo, E.M., Ingrand, P., Gil, M., Neau, J.P., Ornon, C., Bonnaud, V., Self-consciousness, 2001. Alzheimer's disease. Acta Neurol. Scand. 104 (5), 296–300.

Goel, V., Gold, B., Kapur, S., Houle, S., 1997. The seats of reason? An imaging study of deductive and inductive reasoning. Neuroreport 8 (5), 1305–1310.

Goel, V., Grafman, J., Sadato, N., Hallett, M., 1995. Modeling other minds. Neuroreport 6 (13), 1741–1746.

Graham, K.S., Lee, A.C., Brett, M., Patterson, K., 2003. The neural basis of autobiographical and semantic memory: new evidence from three PET studies. Cogn. Affect Behav. Neurosci. 3 (3), 234–254.

Greenberg, D.L., Rubin, D.C., 2003. The neuropsychology of autobiographical memory. Cortex 39 (4–5), 687–728.

Greene, J.D., Hodges, J.R., Baddeley, A.D., 1995. Autobiographical memory and executive function in early dementia of Alzheimer type. Neuropsychologia 33 (12), 1647–1670.

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., Hodges, J.R., 2002. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. Brain 125 (Pt 4), 752–764.

Grober, E., Buschke, H., Crystal, H., Bang, S., Dresner, R., 1988. Screening for dementia by memory testing. Neurology 38 (6), 900–903.

Gutchess, A.H., Kensinger, E.A., Schacter, D.L., 2007. Aging, self-referencing, and medial prefrontal cortex. Social Neurosci. 2, 117–133.

Hay, J.F., Jacoby, L.L., 1999. Separating habit and recollection in young and older adults: effects of elaborative processing and distinctiveness. Psychol. Aging 14 (1), 122–134.

Henson, R.N., Rugg, M.D., Shallice, T., Josephs, O., Dolan, R.J., 1999. Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. J. Neurosci. 19 (10), 3962–3972.

Herholz, K., Salmon, E., Perani, D., Baron, J.C., Holthoff, V., Frolich, L., Schonknecht, P., Ito, K., Mielke, R., Kalbe, E., Zundorf, G., Delbeuck, X., Pelati, O., Anchisi, D., Fazio, F., Kerrouche, N., Desgranges, B., Eustache, F., Beuthien-Baumann, B., Menzel, C., Schroder, J., Kato, T., Arahata, Y., Henze, M., Heiss, W.D., 2002. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 17 (1), 302–316.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. Br. J. Psychiatry 140, 566–572.

Hynes, C.A., Baird, A.A., Grafton, S.T., 2006. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. Neuropsychologia 44 (3), 374–383.

Johnson, S.C., Baxter, L.C., Wilder, L.S., Pipe, J.G., Heiserman, J.E., Prigatano, G.P., 2002. Neural correlates of self-reflection. Brain 125, 1808–1814.

Johnson, S.C., Saykin, A.J., Baxter, L.C., Flashman, L.A., Santulli, R.B., McAllister, T.W., Mamourian, A.C., 2000. The relationship between fMRI activation and cerebral atrophy: comparison of normal aging and Alzheimer disease. Neuroimage 11 (3), 179–187.

Jorm, A.F., 1994. Disability in dementia: assessment, prevention, and rehabilitation. Disabil. Rehabil. 16 (3), 98–109.

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., Weisenbach, S., Brand, M., Lenz, O., Kessler, J., Luedecke, S., Ortelli, P., Herholz, K., 2005. Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. Dement. Geriatr. Cogn. Disord. 19 (5–6), 349–356.

Kelley, W.M., Macrae, C.N., Wyland, C.L., Caglar, S., Inati, S., Heatherton, T.F., 2002. Finding the self? An event-related fMRI study. J. Cogn. Neurosci. 14 (5), 785–794.

Kircher, T.T., Senior, C., Phillips, M.L., Benson, P.J., Bullmore, E.T., Brammer, M., Simmons, A., Williams, S.C., Bartels, M., David, A.S., 2000. Towards a functional neuroanatomy of self-processing: effects of faces and words. Brain Res.: Cogn. Brain Res. 10 (1–2), 133–144.

Klein, S.B., Cosmides, L., Costabile, K.A., 2003. Preserved knowledge of self in a case of Alzheimer's dementia. Soc. Cogn. 21 (2), 157–165.

Klein, S.B., Loftus, J., Kihlstrom, J.F., 1996. Self-knowledge of an amnesic patient: toward a neuropsychology of personality and social psychology. J. Exp. Psychol. Gen. 125 (3), 250–260.

Klein, S.B., Rozendal, K., Cosmides, L., 2002. A social-cognitive neuroscience analysis of the self. Soc. Cogn. 20 (2), 105–135.

Levine, B., Freedman, M., Dawson, D., Black, S., Stuss, D., 1999. Ventral frontal contribution to self-regulation: convergence of episodic memory and inhibition. Neurocase 5, 263–275.
Levine, B., Turner, G.R., Tisserand, D., Hevenor, S.J., Graham, S.J., McIntosh, A.R., 2004. The functional neuroanatomy of episodic and semantic autobiographical remembering: a prospective functional MRI study. J. Cogn. Neurosci. 16 (9), 1633–1646.
Maguire, E.A., Frith, C.D., Morris, R.G., 1999. The functional neuroanatomy of comprehension and memory: the importance of prior knowledge. Brain 122 (Pt 10), 1839–1850.
Majerus, S., Bastin, C., Poncelet, M., Van der Linden, M., Salmon, E., Collette, F., Maquet, P., 2007. Short-term memory and the left intraparietal sulcus: focus of attention? Further evidence from a face short-term memory paradigm. Neuroimage 35 (1), 353–367.
Marcel, A.J., Tegner, R., Nimmo-Smith, I., 2004. Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. Cortex 40 (1), 19–40.
Maril, A., Simons, J.S., Mitchell, J.P., Schwartz, B.L., Schacter, D.L., 2003. Feeling-of-knowing in episodic memory: an event-related fMRI study. Neuroimage 18 (4), 827–836.
Marshall, G.A., Kaufer, D.I., Lopez, O.L., Rao, G.R., Hamilton, R.L., DeKosky, S.T., 2004. Right prosubiculum amyloid plaque density correlates with anosognosia in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 75 (10), 1396–1400.
Mattis, S., 1976. Mental status examination for organic mental syndrome in the elderly patients. In: Bellack, L., Karasu, B. (Eds.), Geriatric Psychiatry. Grune & Stratton, New York, pp. 77–121.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34 (7), 939–944.
Migliorelli, R., Teson, A., Sabe, L., Petracca, G., Petracchi, M., Leiguarda, R., Starkstein, S.E., 1995. Anosognosia in Alzheimer's disease: a study of associated factors. J. Neuropsychiatry Clin. Neurosci. 7 (3), 338–344.
Mimura, M., Yano, M., 2006. Memory impairment and awareness of memory deficits in early-stage Alzheimer's disease. Rev. Neurosci. 17 (1–2), 253–266.
Mitchell, J.P., Macrae, C.N., Banaji, M.R., 2004. Encoding-specific effects of social cognition on the neural correlates of subsequent memory. J. Neurosci. 24 (21), 4912–4917.
Ochsner, K.N., Beer, J.S., Robertson, E.R., Cooper, J.C., Gabrieli, J.D., Kihsltrom, J.F., D'Esposito, M., 2005. The neural correlates of direct and reflected self-knowledge. Neuroimage 28 (4), 797–814.
Ochsner, K.N., Knierim, K., Ludlow, D.H., Hanelin, J., Ramachandran, T., Glover, G., Mackey, S.C., 2004. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J. Cogn. Neurosci. 16 (10), 1746–1772.
Parkin, A.J., Walter, B.M., 1992. Recollective experience, normal aging, and frontal dysfunction. Psychol. Aging 7 (2), 290–298.
Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De la Sayette, V., Eustache, F., 2003. Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. Brain 126 (Pt 10), 2203–2219.
Prull, M.W., Dawes, L.L., Martin III, A.M., Rosenberg, H.F., Light, L.L., 2006. Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. Psychol. Aging 21 (1), 107–118.
Prvulovic, D., Van de Ven, V., Sack, A.T., Maurer, K., Linden, D.E., 2005. Functional activation imaging in aging and dementia. Psychiatry Res. 140 (2), 97–113.
Ranganath, C., Yonelinas, A.P., Cohen, M.X., Dy, C.J., Tom, S.M., D'Esposito, M., 2004. Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia 42 (1), 2–13.
Rankin, K.P., Baldwin, E., Pace-Savitsky, C., Kramer, J.H., Miller, B.L., 2005. Self awareness and personality change in dementia. J. Neurol. Neurosurg. Psychiatry 76 (5), 632–639.
Rauchs, G., Piolino, P., Meézenge, F., Landeau, B., Lalevée, C., Pélerin, A., Viader, F., de la Sayette, V., Eustache, F., Desgranges, B., 2007. Autonoetic consciousness in Alzheimer's disease: neuropsychological and PET findings using an episodic learning and recognition task. Neurobiol. Aging 28 (9), 1410–1420.
Ries, M.L., Schmitz, T.W., Kawahara, T.N., Torgerson, B.M., Trivedi, M.A., Johnson, S.C., 2006. Task-dependent posterior cingulate activation in mild cognitive impairment. Neuroimage 29 (2), 485–492.
Robert, P.H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., Caci, H., Borg, M., Brocker, P., Bedoucha, P., 2002. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease. Parkinson's disease and mild cognitive impairment. Int. J. Geriatr. Psychiatry 17 (12), 1099–1105.
Rubia, K., Smith, A.B., Brammer, M.J., Taylor, E., 2003. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 20 (1), 351–358.
Ruby, P., Decety, J., 2001. Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nat. Neurosci. 4 (5), 546–550.
Ruby, P., Decety, J., 2004. How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. J. Cogn. Neurosci. 16 (6), 988–999.
Ruby, P., Decety, J., 2003. What you believe versus what you think they believe: a neuroimaging study of conceptual perspective-taking. Eur. J. Neurosci. 17 (11), 2475–2480.
Ruby, P., Legrand, D., 2008. Neuroimaging the Self? In: Hagard, P., Rossetti, P. (Eds.), Sensorimotor Foundations of Higher Cognition. Attention & Performance Meeting, vol. XXII. Oxford University Press, Oxford, pp. 293–317.
Ruby, P., Schmidt, C., Hogge, M., D'Argembeau, A., Collette, F., Salmon, E., 2007. Social mind representation: where does it fail in frontotemporal dementia? J. Cogn. Neurosci. 19 (4), 671–683.
Salmon, E., Lespagnard, S., Marique, P., Herhol, K., Perani, D., Holthoff, V., Kalbe, E., Anchisi, D., Adam, S., Garraux, G., 2005a. Cerebral metabolic correlates of four dementia scales in Alzheimer's disease. J. Neurol. 252, 283–290.
Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., Delbeuck, X., Beuthien-Baumann, B., Pelati, O., Lespagnard, S., Collette, F., Garraux, G., 2006. Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. Hum. Brain Mapp. 27 (7), 588–597.
Salmon, E., Ruby, P., Perani, D., Kalbe, E., Laureys, S., Adam, S., Collette, F., 2005b. Two aspects of impaired consciousness in Alzheimer's disease. Prog. Brain Res. 150, 287–298.
Schaefer, A., Collette, F., Philippot, P., van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Maquet, P., Luxen, A., Salmon, E., 2003. Neural correlates of "hot" and "cold" emotional processing: a multilevel approach to the functional anatomy of emotion. Neuroimage 18 (4), 938–949.
Schmitz, T.W., Kawahara-Baccus, T.N., Johnson, S.C., 2004. Metacognitive evaluation, self-relevance, and the right prefrontal cortex. Neuroimage 22 (2), 941–947.
Souchay, C., Isingrini, M., Gil, R., 2002. Alzheimer's disease and feeling-of-knowing in episodic memory. Neuropsychologia 40 (13), 2386–2396.
Svoboda, E., McKinnon, M.C., Levine, B., 2006. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 44 (12), 2189–2208.
Takahashi, H., Yahata, N., Koeda, M., Matsuda, T., Asai, K., Okubo, Y., 2004. Brain activation associated with evaluative processes of guilt and embarrassment: an fMRI study. Neuroimage 23 (3), 967–974.
Vasterling, J.J., Seltzer, B., Watrous, W.E., 1997. Longitudinal assessment of deficit unawareness in Alzheimer's disease. Neuropsychiatry Neuropsychol. Behav. Neurol. 10 (3), 197–202.
Viard, A., Piolino, P., Desgranges, B., Chetelat, G., Lebreton, K., Landeau, B., Young, A., De La Sayette, V., Eustache, F., 2007. Hippocampal acti-

vation for autobiographical memories over the entire lifetime in healthy aged subjects: an fMRI study. Cereb. Cortex.
Vogel, A., Hasselbalch, S.G., 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 (3), 238–246.
Vogeley, K., Bussfeld, P., Newen, A., Herrmann, S., Happe, F., Falkai, P., Maier, W., Shah, N.J., Fink, G.R., Zilles, K., 2001. Mind reading: neural mechanisms of theory of mind and self-perspective. Neuroimage 14 (1 Pt 1), 170–181.
Vogeley, K., May, M., Ritzl, A., Falkai, P., Zilles, K., Fink, G.R., 2004. Neural correlates of first-person perspective as one constituent of human self-consciousness. J. Cogn. Neurosci. 16 (5), 817–827.
Vuilleumier, P., 2004. Anosognosia: the neurology of beliefs and uncertainties. Cortex 40 (1), 9–17.
Wagner, A.D., Shannon, B.J., Kahn, I., Buckner, R.L., 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn. Sci. 9 (9), 445–453.
Westerberg, C.E., Paller, K.A., Weintraub, S., Mesulam, M.M., Holdstock, J.S., Mayes, A.R., Reber, P.J., 2006. When memory does not fail: familiarity-based recognition in mild cognitive impairment and Alzheimer's disease. Neuropsychology 20 (2), 193–205.
Wilson, T.D., Dunn, E.W., 2004. Self-knowledge: its limits, value, and potential for improvement. Annu. Rev. Psychol. 55, 493–518.
Yonelinas, A.P., Otten, L.J., Shaw, K.N., Rugg, M.D., 2005. Separating the brain regions involved in recollection and familiarity in recognition memory. J. Neurosci. 25 (11), 3002–3008.
Zysset, S., Huber, O., Ferstl, E., von Cramon, D.Y., 2002. The anterior frontomedian cortex and evaluative judgment: an fMRI study. Neuroimage 15 (4), 983–991.