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CHAPTER 21

Two aspects of impaired consciousness in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a degenerative dementia characterized by different aspects of impaired consciousness. For example, there is a deficit of controlled processes that require conscious processing of information. Such an impairment is indexed by decreased performances at controlled cognitive tasks, and it is related to reduced brain metabolic activity in a network of frontal, posterior associative, and limbic regions. Another aspect of impaired consciousness is that AD patients show variable levels of anosognosia concerning their cognitive deficits. A discrepancy score between patient's and caregiver's assessment of cognitive functions is one of the most frequently used measures of anosognosia. A high discrepancy score has been related to impaired activity in the superior frontal sulcus and the parietal cortex in AD. Anosognosia for cognitive deficits in AD could be partly explained by impaired metabolism in parts of networks subserving self-referential processes (e.g., the superior frontal sulcus) and perspective-taking (e.g., the temporoparietal junction). We hypothesize that these patients are impaired in the ability to see themselves with a third-person perspective (i.e., being able to see themselves as other people see them).

Introduction

Alzheimer's disease (AD) is the most common cause of dementia among people aged 65 and older. About 3% of men and women aged 65 to 74 have AD, and nearly half of those aged 85 and older may have the disease. AD is clinically characterized by a dementia syndrome. Current features for dementia include a deterioration in cognitive functions, sufficient to impair daily living activities (APA, 1994). Neuropsychological studies have demonstrated that AD patients show impairment in controlled cognitive processes, while automatic activities may be more preserved (Fabrigoule et al., 1998). It is frequently observed that AD patients fail to consciously recollect information whereas they provide target memories in implicit conditions. This constitutes a first aspect of impaired consciousness in AD.

Other characteristics of dementia include personality change and altered judgment (APA, 1987). Behavioral and psychological impairments are well described in AD (Cummings et al., 1994; Neary et al., 1998). More specifically, lack of awareness for self-cognitive or behavioral difficulties (anosognosia for deterioration) is frequently observed in the disease. However, assessing anosognosia is a difficult task, and patients may show different degrees of awareness in different domains (e.g., reasoning, memory, and social behavior) (Fig. 1).

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Fig. 1. "Alzheimer, maybe, but I am still a genius!." Demented patient with anosognosia for cognitive deficit (Reproduced with permission – copyright C. Laureys).

The aim of this chapter is to discuss possible relationships between abnormal brain function in patients with AD and (i) decreased controlled access to information in memory and (ii) measures of anosognosia concerning cognitive impairment.

Controlled and automatic processes in AD

It is widely acknowledged that AD can selectively impair specific cognitive processes early in the course of the disease, while others remain relatively preserved until the pathology becomes severe (Collette et al., 2003). It was suggested that controlled processes (requiring attentional resources) are affected at an early stage while automatic processes are relatively more preserved (Jorm, 1986). The hypothesis of controlled processes impairment was explicitly explored in recent studies (Fabrigoule et al., 1998; Salthouse and Becker, 1998; Amieva et al., 2000). For example, Fabrigoule (1998) longitudinally studied cognitive performances in a large sample of 1,159 healthy elderly subjects. After 2 years, 16 of these subjects were diagnosed as having AD. A principal component analysis coupled with a logistic regression analysis showed that one factor explained 45% of the variance in test performance and constituted a good predictor of the risk of developing AD. The authors proposed, from post-hoc analyses, that this factor corresponds to the controlled or executive processes of the tasks. Controlled and automatic processes can be explored more directly in the memory domain by using explicit and implicit memory tasks, respectively. AD is associated with impairments in explicit (i.e., controlled) memory tasks such as free and cued recall or recognition (Salmon, 2000). However, the results related to implicit (i.e., automatic) memory tasks are more controversial. Some reviews of the literature (Meiran and Jelicic, 1995; Fleischman and Gabrieli, 1998) showed that AD patients often present a preserved priming effect on implicit tasks such as word and picture identification or lexical decisions, but they are frequently impaired on priming tasks that require implicit retrieval of conceptual information such as word association, category-exemplar generation, and word-stem completion. One reason invoked by various authors to explain these ambiguous results is that healthy participants may use explicit retrieval strategies when performing an ostensibly implicit retrieval task (Vaidya et al., 1996). This use of explicit strategies might artificially increase the "priming effect" for conceptual information in normal controls but not in AD patients, considering their explicit memory deficit (Fleischman and Gabrieli, 1998). This contamination interpretation is in line with Jacoby's view that there are no "process-pure" memory tasks (Jacoby et al., 1992).

Behavioral measures of controlled and automatic processes: the process dissociation procedure

Jacoby hypothesized that there are two independent ways to retrieve information in memory, i.e., controlled and automatic processes, and he proposed an elegant method, the process dissociation procedure (PDP), to separate the degree to which controlled and automatic processes contribute to performance in a single memory task (Yonelinas and Jacoby, 1995). This procedure comprises two conditions: one condition in which controlled and automatic processes act in concert to influence

performance in the same way (the *inclusion* condition where both processes converge to produce the correct answer), and the other in which controlled and automatic processes have opposing effects (the *exclusion* condition). Considering that automatic and controlled processes contribute independently to performance, an equation can be written that represents how the two processes act to determine performance in each condition. On the basis of these two equations, the contributions of automatic and controlled processes to task performance can be estimated using simple algebra (Fig. 2; note that other measurement models exist and that the specific equations assume that automatic and controlled processes are independent from each other).

Several studies have applied PDP in order to explore automatic and controlled processes in AD, especially in the domain of memory. In particular, a word-stem completion task was administered to early AD patients, applying the PDP (Koivisto et al., 1998). In each inclusion and exclusion condition, subjects were presented with word-stems and were told to use them as cues for recollecting a word that had previously been studied (e.g., *flow*, — as a cue to recall *flower*, Fig. 2). In the inclusion condition, subjects were asked to complete a stem with a previously studied word or, if they were unable to do so, to use the first word that came to mind. Therefore, in this condition, subjects could correctly complete a stem with an earlier studied word either because they consciously recollected it having seen the word before (probability C), or because it was the first word that came to mind automatically (probability A), without any conscious recollection that the word had been presented earlier ($1–C$). Thus, the probability of completing a stem in the inclusion condition can be represented as inclusion $= C+A\ (1–C)$. By contrast, in the exclusion condition, subjects were asked to complete the stem with a new word that had not been encountered during the study phase and to avoid (exclude) words that had been studied. In this condition, subjects might incorrectly complete a word that had been studied earlier only if that word came automatically to mind (A), without any "conscious", controlled recollection that it had been presented earlier ($1–C$). Thus, the probability of producing an error (i.e., completing a stem with a word that had been studied earlier) in the exclusion condition can be represented as exclusion $= A\ (1–C)$. Following Jacoby, the contribution of controlled ("conscious") processes in the task can be estimated by subtracting the probability of responding with a studied word in the exclusion condition from the probability of responding with an old (i.e., studied) word in the inclusion condition. Once an estimate of controlled processes has been obtained, the contribution of automatic processes corresponds to the

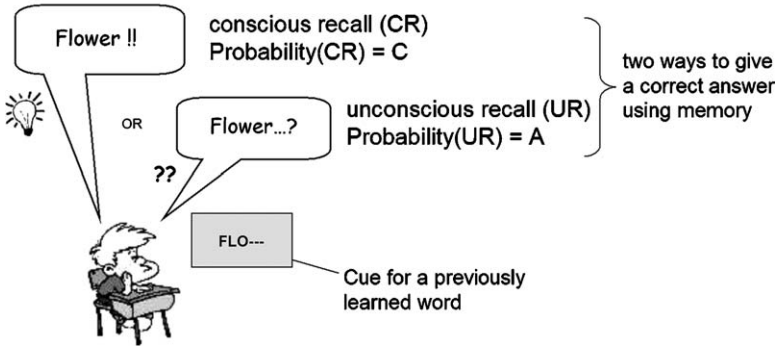

Fig. 2. Illustration of the process dissociation procedure proposed by Jacoby (1992). Inclusion condition: "complete the stem with a word presented during the learning stage". Score (Inclusion) = Probability ("Flower") $= C+A(1-C)$. Exclusion condition: "complete the stem with a word, which was not presented during the learning stage". If the subject erroneously completes the stem with the studied word, the score (Exclusion) = Probability ("Flower") $= A(1-C)$. Estimation of Conscious process contribution to recall: C = score (inclusion) – score (exclusion), Estimation of Unconscious process contribution to recall: A = score (exclusion)/$(1-C)$.

probability of completing a stem with the studied word in the exclusion condition (exclusion score) divided by one minus the probability of consciously completing a stem with the studied word in the inclusion condition ($1-C$).

A severe impairment of controlled memory processes was reported in mild and moderate AD patients (Koivisto et al., 1998). More specifically, in AD patients, no difference was found between the inclusion and exclusion conditions in terms of the probability of completion with old words. On the other hand, the estimates of automatic processes were similar in AD patients and control subjects, suggesting that automatic memory processes were preserved in AD. However, data suggested that patients and controls may have used different response strategies in the two conditions. Using a similar stem completion task, another study showed that although the AD patients' performance on the word-stem completion memory task was strongly supported by automatic memory processes, the control group relied on automatic processes even more (Knight, 1998). This suggested that automatic processes were also impaired in AD, even if this impairment was not as great as that of controlled processes. However, in this study, the task was very easy for the control subjects (as suggested by a ceiling effect in the inclusion and a floor effect in the exclusion condition), leading to an overestimation of the contribution made by automatic processes in this group. Moreover, it was not possible to guarantee that the AD patients understood the task instructions, particularly in the exclusion condition (Curran and Hintzman, 1995). Difficulties understanding instructions may produce differential biases in responding across the inclusion and exclusion conditions.

To sum up, the PDP seems to be a useful tool to directly explore the contribution made by controlled and automatic processes in AD. However, the studies that have used this paradigm to test memory functioning tend to be either unclear or somewhat controversial, particularly concerning the status of automatic processes (preserved or not preserved). A recent study verified the integrity of automatic processes in AD by designing a memory task that limited the methodological and psychometric problems affecting previous experiments applying the PDP approach (Adam et al., 2005). The results confirmed the marked deterioration in controlled processes, while automatic memory processes were preserved in AD patients compared to control subjects. Moreover, analyses showed a positive correlation between controlled processes and disease progression as measured by the mini mental state examination (MMSE; Folstein et al., 1975). These results should be interpreted by considering that MMSE principally measures controlled processes, as this scale includes items involving effortful attentional tasks (e.g., immediate and episodic memory, mental calculation).

A potential area where the demonstrated distinction between controlled and automatic processes could be applied is the cognitive rehabilitation of AD patients. One would predict that AD patients, whose controlled processes are impaired, would behave better when they can rely on automatic procedures (Jorm, 1986). From this perspective, it is, for example, possible to promote specific learning procedures to allow early AD patients to automatically use a cellular phone (Lekeu et al., 2002).

Neural substrate of controlled processes

Which are the neurobiological substrates for controlled processes allowing access to memories? There is a tight coupling between controlled processes and executive functions. In Baddeley's model of working memory (1992), the central executive is assumed to be an attentional control system. It was recently suggested that executive functions (or "top-down" controlled processes) rely on a distributed cerebral network including both anterior and posterior cerebral areas (Weinberger, 1993; Morris, 1994; Collette et al., 1999a, 2002). Moreover, recollection of episodic memories (controlled retrieval compared to simple familiarity for information) was related to activation in prefrontal, parietal, and posterior cingulate regions in normal subjects (Henson et al., 1999). In AD, performances at diverse executive tasks were related either to frontal activity for phonemic

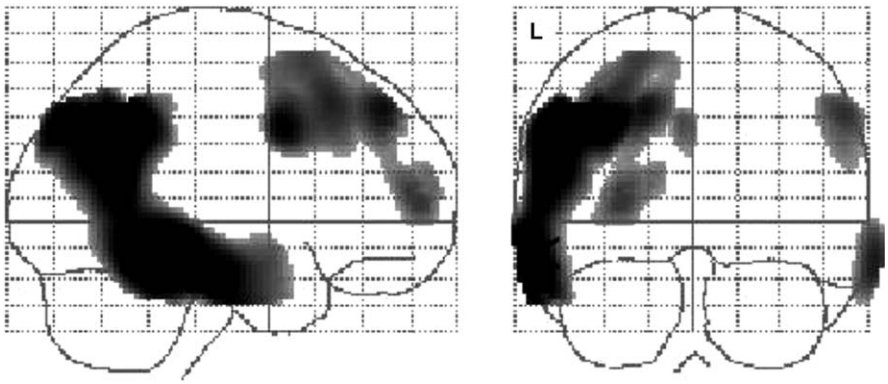

Fig. 3. Decreased metabolism in temporo-parietal and frontal associative cortices is related to severity of the dementia in AD.

fluency, or to posterior associative cortices for dual tasks (Collette et al., 1999c). From this perspective, two interpretations may be proposed to account for the controlled process deficits of AD patients: they could originate either from multiple neuropathological and metabolic changes in both anterior and posterior cerebral areas or from a (partial) disconnection between the anterior and posterior cortical areas, leading to a less efficient transfer of information between these regions. Consistent with the first interpretation, global dementia scores, which essentially depend on controlled processes, are related to decreased metabolism in both associative temporoparietal and frontal cortices in AD (Salmon et al., 2005) (see Fig. 3).

Consistent with the second interpretation, a number of neuropathological, neuropsychological, and neuroimaging studies have suggested that AD can be characterized as a disconnection syndrome (Azari et al., 1992; Leuchter et al., 1992; Morris, 1994; Collette et al., 2002; Lekeu et al., 2003a). Thus, loss of synaptic contacts in associative cortices and limbic structures would interrupt long connecting pathways in AD (Hyman et al., 1984; Pearson et al., 1985). The relative preservation of automatic processes in AD patients would mean that these processes are subserved by circumscribed cortical areas that are less affected by disconnection in the early stages of the disease. As the disease progresses, the neuropathological changes would affect more cortical areas (and local connections between them) and consequently also alter automatic processes. Such a hypothesis of successive impairment of controlled and automatic processes has been proposed to explain working memory deficits in AD (Collette et al., 1999b).

Frontoparietal associative cortices related to controlled processes may constitute a major component of a cerebral workspace, where attentional display of information would allow active and controlled recollection of information (Dehaene and Naccache, 2001). However, lesions in other structures, such as the hippocampus, could also explain impairment of conscious (i.e., controlled) retrieval of information in AD. Supportive to this hypothesis, a study required AD patients to learn words that they subsequently had to recognize among distractors (Lekeu et al., 2003b): an accuracy score (hits minus false alarms), taken as a measure of ''conscious/controlled retrieval'' (recollection), correlated with residual metabolism in the hippocampus. In neuroimaging studies in control subjects, medial temporal activation is known to be greater for explicit cued recall using word stem than for a priming task using similar stems, suggesting a role for hippocampus in conscious access to memories (Squire, 1992).

Anosognosia in AD

Anosognosia, lack of awareness or loss of insight, is used interchangeably to describe the impaired judgment of AD subjects concerning their own cognition, mood, behavior, or daily activities.

Behavioral measures of anosognosia in AD

The study of anosognosia requires to choose an instrument to measure loss of insight into a particular domain of interest. In experimental conditions, evidence of unawareness of memory dysfunction is provided in AD patients when their predictions overestimate their memory performance in a subsequent retrieval task (McGlynn and Schacter, 1989). Questionnaires for assessing anosognosia in dementia are frequently used in the literature, and a discrepancy score is calculated between answers obtained from the patient and from a caregiver (Migliorelli et al., 1995a). Self-rating of cognitive deficits is also proposed as an index of cognitive unawareness, because AD patients report cognitive impairment that they frequently do not find particularly abnormal for their age (Cummings et al., 1995). Loss of insight may be evaluated by the clinician, on the basis of patient answers to questions probing awareness of cognitive deficits (expert judgment), or by caregivers assessing the frequency of behavioral manifestations of unawareness in everyday life (Derouesne et al., 1999). While most patients with mild cognitive impairment (MCI) tend to overestimate their cognitive deficits when compared to their caregiver's assessment, AD patients in early stages of the disease with similar MMSE scores underestimate their cognitive dysfunction (Kalbe et al., 2005). Accordingly, underestimation of cognitive difficulties (compared to caregiver's assessment) is considered as a risk factor for conversion from MCI to AD (Tabert et al., 2002). Several demographic, clinical, and neuropsychological parameters were proposed to be associated with unawareness for self-cognitive deficits in AD. Lack of awareness of AD patients was correlated to dementia severity in most, but not all studies (Sevush and Leve, 1993; McDaniel et al., 1995; Sevush, 1999; Zanetti et al., 1999; Gil et al., 2001). The relationship between anosognosia and depression remains a matter of discussion (Sevush and Leve, 1993; Cummings et al., 1995). Differences in assessment of anosognosia and definition of depression might explain these discrepancies. Patients with dysthymia would have a significantly better awareness of intellectual deficits than patients with major or no depression (Migliorelli et al., 1995b). Stepwise regression analysis showed that insight into functional impairment was (positively) associated with depression and anxiety factor scores, and (negatively) with agitation and disinhibition factor scores (Harwood et al., 2000). Specific relationships were sought between lack of awareness of cognitive deficits and performance on neuropsychological tests. Anosognosia in AD subjects was associated, in some but not all studies, with memory impairment, reflected, for example, by intrusions (i.e., erroneous selection of non-target items) in recognition tasks (Reed et al., 1993; Dalla Barba et al., 1995). A relationship was frequently suggested between lack of awareness of cognitive dysfunction and impairment in specific "frontal" tests (Lopez et al., 1994; Michon et al., 1994; Dalla Barba et al., 1995; Ott et al., 1996). All those parameters may be viewed as confounding factors, that contribute to, but do not yet explain, anosognosia in dementia. Moreover, they show that different dimensions exist in anosognosia (Agnew and Morris, 1998).

To further discuss anosognosia for cognitive deficits in early stages of dementia, a review of the different components of the "unified self" proposed by Klein et al. (2002) might be useful. These authors suggested that the self can be conceptualized as a complex knowledge structure subserved by at least two neurally and functionally dissociable components: episodic memory and semantic memory. Episodic memory of one's own life (i.e., episodic autobiographical memory) is certainly impaired in AD subjects (Greene et al., 1995; Piolino et al., 2003). So, patients will have a decrease of their autonoetic experiences, i.e., those events that patients have personally lived, but cannot recollect in a precise contextual format that makes them unique subjective experiences (Wheeler et al., 1997; Tulving, 2002). However, deficits in episodic memory are not sufficient to explain the different degrees of unawareness for self-cognitive deficits in AD because numerous patients with severe amnesia from other etiologies do not show anosognosia. Semantic personal knowledge seems to be also impaired in AD, however, it is difficult to dissociate the respective influences of semantic and

episodic memory disturbances (Kazui et al., 2003). Representation of one's own personality traits might be a specific (and independent) aspect of semantic knowledge (Klein et al., 2002). In a study on moderately severe AD patients, awareness of behavioral and psychological problems was relatively preserved compared to awareness of cognitive impairment (Kotler-Cope and Camp, 1995). Such an observation, however, might reflect the natural evolution of AD and not the different levels of anosognosia in different domains, because AD patients have relatively few behavioral troubles compared to cognitive deficits in a moderate stage of dementia. Indeed, in a patient with severe AD, it was shown that knowledge of own personality traits failed to be updated (Klein et al., 2003). Experience of personal agency has not been directly assessed in AD, but experience of continuity through time is impaired since AD patients are known to experience a temporal gradient for loss of autobiographical memories (Greene et al., 1995). Ability to reflect on one's own thoughts and experience is an important component of the self that appears to be impaired in AD patients, who deny any cognitive problem even when they are totally unable to remember any recent personal event.

The neural correlates of anosognosia for cognitive impairment in AD

Different brain regions were implicated in anosognosia for different neurological disorders, such as neglect, hemiparesis, aphasia, cortical blindness, or profound amnesia. Lack of awareness was reported in patients with diverse frontal lobe pathologies (McGlynn and Schacter, 1989). In the functional imaging literature, medial prefrontal and posterior cingulate cortices were shown to be part of a neural network subserving self-reflective thoughts in normal subjects (Johnson et al., 2002; Kelley et al., 2002). Decreased activity in the ventromedial prefrontal cortex and the temporal poles is characteristic of frontotemporal dementia (FTD; Salmon et al., 2003) and this might explain impairment of self-reflection and early loss of insight into behavioral disturbances in these patients. On the contrary, there is an early decrease of activity in posteromedial cortices (posterior cingulate and precuneus; Fig. 4A) in AD patients (Minoshima et al., 1994). Posterior cingulate hypometabolism was related to dementia severity in AD (Fig. 4B; Salmon et al., 2000) and it was involved in episodic, semantic, and working memory in control populations (Petrides et al., 1993; Fletcher et al., 1998;

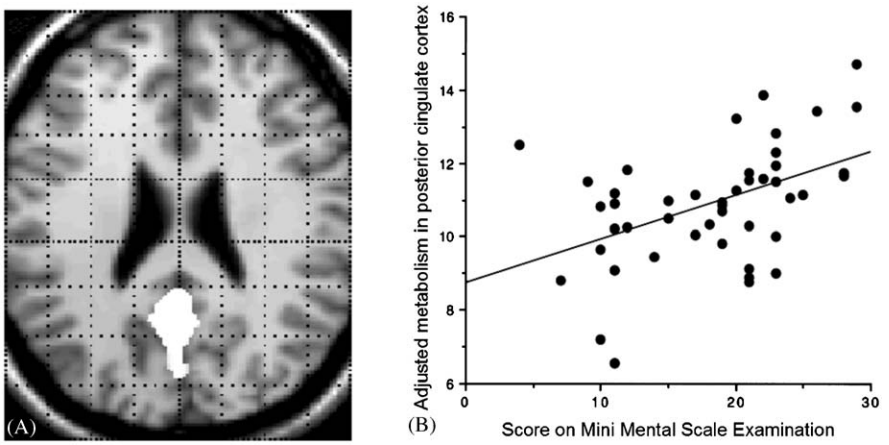

Fig. 4. (A) Early decrease of activity in posteromedial areas (encompassing posterior cingulate cortex and precuneus) in patients with AD. (B) Linear correlation between dementia severity (score on mini mental state examination) and metabolism in posterior cingulate cortex (area 31, coordinates: $x = 0$, $y = -56$, $z = 28$ mm) in AD. (From Salmon et al., 2000, with permission.)

Henson et al., 1999; Maguire and Mummery, 1999). Posteromedial cortices (in relation with hippocampal structures) are thought to be involved in the episodic integration of interoceptive and exteroceptive information required for conscious/controlled processing (Maguire et al., 1999; Salmon, 2003). Accordingly, in healthy subjects, posterior cingulate activity is low during executive processes, which are driven by external stimuli (without self-reference) (Salmon et al., 1999; Gusnard et al., 2001). So, posteromedial cortices are mainly related to personal memories and they would be poorly recruited in self-referential tasks by AD patients due to their episodic memory impairment.

Studies relating anosognosia to brain activity have shown a decrease of right lateral frontal and parietal activity in AD patients with anosognosia (Leys et al., 1989; Starkstein et al., 1995; Derouesne et al., 1999). In a theoretical model, the ''conscious awareness system'' was suggested to depend on inferior parietal and posterior cingulate cortex (McGlynn and Schacter, 1989). It has an output link to an executive system housed in the frontal lobe. Frontal damage would be associated with unawareness of complex deficits, such as difficulties in problem solving or behavioral changes. In a recent study, a cognitive discrepancy score (difference between patient's and caregiver's assessment) was inversely related to metabolism in temporoparietal junctions and superior frontal sulci in a large population of AD patients (Salmon et al., 2004). In other words, the more the patient underestimates his cognitive impairment, the lower the metabolism in temporoparietal junctions. It is noteworthy that the temporoparietal junction and lateral prefrontal areas are part of the associative cortices where metabolism is characteristically impaired in AD (Herholz et al., 2002). This would suggest that a relative anosognosia for cognitive impairment is intrinsic to AD pathology and would also explain the trend to greater anosognosia with greater severity of dementia (Zanetti et al., 1999).

The temporoparietal cortex and superior frontal sulcus have been previously reported in self-referential processes (Wicker et al., 2003). For example, lesions in the temporoparietal junction have been related to mirrored self-misidentification in demented patients (Breen et al., 2001). In healthy subjects, activation of temporoparietal junctions was observed in neuroimaging studies when contrasting first- and third-person perspectives in various types of tasks involving: intention attribution (Vogeley et al., 2001), 3D visuospatial perspective (Vogeley et al., 2004), action imagination (Ruby and Decety, 2001), truthfulness judgment (Ruby and Decety, 2003), or emotional assessment (Ruby and Decety, 2004). It has been demonstrated that stimulation of the right temporoparietal junction in humans can induce out of body experiences, in other words, a visual observation of the self with a third-person perspective (Blanke et al., 2002; Blanke, this volume). According to these results, it was suggested that the temporoparietal junction participates to the self/other distinction process required during perspective-taking (Ruby and Decety, 2004). One reason which makes this region a good candidate for such a role is that it houses the praxicon, a lexicon of representations concerning human actions (Peigneux et al., 2001). In the right hemisphere, the temporoparietal junction was related to anosognosia of hemiplegia (Venneri and Shanks, 2004). The praxicon is essential to compare self and other's familiar actions, and AD patients with anosognosia seem not to be aware of the difference between their impaired abilities and other's normal activities.

The parietal associative cortex related to a discrepancy score in AD may be involved in self-referential processes or may subserve the ''third-person'' knowledge that AD patients have of themselves (Tulving, 1993; Agnew and Morris, 1998; Klein et al., 2003). Accordingly, the right inferior parietal cortex was activated when volunteers had to recall whether an adjective had initially been characterized as fitting their personality (Lou et al., 2004). In that sense, anosognosia assessed by a discrepancy score might be interpreted as an impaired ability to see oneself with a third-person perspective (knowing how other people see yourself), an ability which would correspond to ''the observing self'' defined by Baars (Baars et al., 2003; Baars, this volume). According to this interpretation, one would expect that with the evolution of the disease, AD patients demonstrate impaired perspective taking on others. In line with this hypothesis, severe AD patients have been

shown to become unable to assess other people's personality traits (Klein et al., 2003).

Conclusion

We suggest that specific brain regions are involved in different aspect of impaired consciousness in AD. On the one hand, a network of frontal, posterior associative, and limbic structures was demonstrated to be related to controlled processes that require conscious processing of information. On the other, impaired metabolism in lateral prefrontal and parietal areas was shown to correlate with the discrepancy score between AD patient and caregiver, one of the different measures of anosognosia for cognitive impairment. According to those results, we suggest that anosognosia for cognitive deficits in AD might be partly explained by impaired metabolism in parts of networks subserving self-referential processes (the superior frontal sulcus) and perspective-taking (the temporo-parietal junction). Patients appear to be impaired in the ability to see themselves with a third-person perspective (i.e., knowing how other people see themselves). Models of anosognosia suggest that those regions are only part of a wider cerebral network subserving unawareness of cognitive deficits in AD (Agnew and Morris, 1998).

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References

Adam, S., Van der Linden, M., Collette, F., Lemauvais, L. and Salmon, E. (2005). Further exploration of controlled and automatic memory processes in early Alzheimer's disease. Neuropsychology (in press).

Agnew, S.K. and 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.

Amieva, H., Rouch-Leroyer, I., Fabrigoule, C. and Dartigues, J.F. (2000) Deterioration of controlled processes in the preclinical phase of dementia: a confirmatory analysis. Dement. Geriatr. Cogn. Disord., 11: 46–52.

APA. (1987) Diagnostic and Statistical Manual of Mental Disorders (3rd ed.). American Psychiatric Association, Washington, DC.

APA. (1994) Diagnostic and Statistical Manual of Mental Disorders (4th ed.). American Psychiatric Association, Washington, DC.

Azari, N.P., Rapoport, S.I., Grady, C.L., Schapiro, M.B., Salerno, J.A., Gonzalez-Aviles, A., et al. (1992) Patterns of interregional correlations of cerebral glucose metabolism rates in patients with dementia of the Alzheimer type. Neurodegeneration, 1: 101–111.

Baars, B.J., Ramsoy, T.Z. and Laureys, S. (2003) Brain conscious experience and the observing self. Trends Neurosci., 26: 671–675.

Baddeley, A. (1992) Working memory. Science, 255: 556–559.

Blanke, O., Ortigue, S., Landis, T. and Seeck, M. (2002) Stimulating illusory own-body perceptions. Nature, 419: 269–270.

Breen, N., Caine, D. and Coltheart, M. (2001) Mirrored-self misidentification: two cases of focal onset dementia. Neurocase, 7: 239–254.

Collette, F., Salmon, E., Van der Linden, M., Chicherio, C., Belleville, S., Degueldre, C., et al. (1999a) Regional brain activity during tasks devoted to the central executive of working memory. Brain Res. Cogn. Brain Res., 7: 411–417.

Collette, F., Van der Linden, M., Bechet, S. and Salmon, E. (1999b) Phonological loop and central executive functioning in Alzheimer's disease. Neuropsychologia, 37: 905–918.

Collette, F., Van der Linden, M., Delrue, G. and Salmon, E. (2002) Frontal hypometabolism does not explain inhibitory dysfunction in Alzheimer disease. Alzheimer Dis. Assoc. Disord., 16: 228–238.

Collette, F., Van der Linden, M., Juillerat, A.C. and Meulemans, T. (2003) A cognitive neuropsychological approach
to Alzheimer's disease. In: Mulligan R., Van der Linden M. and Juillerat A.C. (Eds.), Clinical Management of Early Alzheimer's Disease. Erlbaum, Mahwah, pp. 35–73.

Collette, F., Van der Linden, M. and Salmon, E. (1999c) Executive dysfunction in Alzheimer's disease. Cortex, 35: 57–72.

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

Cummings, J.L., Ross, W., Absher, J., Gornbein, J. and Hadjiaghai, L. (1995) Depressive symptoms in Alzheimer disease: assessment and determinants. Alzheimer Dis. Assoc. Disord., 9: 87–93.

Curran, T. and Hintzman, D.L. (1995) Violations of the independence assumption in process dissociation. J. Exp. Psychol. Learn Mem. Cogn., 21: 531–547.

Dalla Barba, G., Parlato, V., Iavarone, A. and Boller, F. (1995) Anosognosia, intrusions and 'frontal' functions in Alzheimer's disease and depression. Neuropsychologia, 33: 247–259.

Dehaene, S. and Naccache, L. (2001) Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition, 79: 1–37.

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

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

Fleischman, D.A. and Gabrieli, J.D. (1998) Repetition priming in normal aging and Alzheimer's disease: a review of findings and theories. Psychol. Aging, 13: 88–119.

Fletcher, P.C., Shallice, T. and Dolan, R.J. (1998) The functional roles of prefrontal cortex in episodic memory. I. Encoding. Brain, 121(Pt 7): 1239–1248.

Folstein, M.F., Folstein, S.E. and McHugh, P.R. (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res., 12: 189–198.

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

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

Gusnard, D.A., Akbudak, E., Shulman, G.L. and Raichle, M.E. (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc. Natl. Acad. Sci. USA, 98: 4259–4264.

Harwood, D.G., Sultzer, D.L. and Wheatley, M.V. (2000) Impaired insight in Alzheimer disease: association with cognitive deficits, psychiatric symptoms, and behavioral disturbances. Neuropsychiatry Neuropsychol. Behav. Neurol., 13: 83–88.

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

Herholz, K., Salmon, E., Perani, D., Baron, J.C., Holthoff, V., Frolich, L., et al. (2002) Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage, 17: 302–316.

Hyman, B.T., Van Horsen, G.W., Damasio, A.R. and Barnes, C.L. (1984) Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science, 225: 1168–1170.

Jacoby, L.L., Lindsay, D.S. and Toth, J.P. (1992) Unconscious influences revealed. Attention, awareness, and control. Am. Psychol., 47: 802–809.

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

Jorm, A.F. (1986) Controlled and automatic information processing in senile dementia: a review. Psychol. Med., 16: 77–88.

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., et al. (2005) Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. Dement. Geriatr. Cogn. Disord., 19: 349–356.

Kazui, H., Hashimoto, M., Hirono, N. and Mori, E. (2003) Nature of personal semantic memory: evidence from Alzheimer's disease. Neuropsychologia, 41: 981–988.

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

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

Klein, S.B., Rozendal, K. and Cosmides, L. (2002) A social-cognitive neuroscience analysis of the self. Social Cognition., 20: 105–135.

Knight, R.G. (1998) Controlled and automatic memory process in Alzheimer's disease. Cortex, 34: 427–435.

Koivisto, M., Portin, R., Seinela, A. and Rinne, J. (1998) Automatic influences of memory in Alzheimer's disease. Cortex, 34: 209–219.

Kotler-Cope, S. and Camp, C.J. (1995) Anosognosia in Alzheimer disease. Alzheimer Dis. Assoc. Disord., 9: 52–56.

Lekeu, F., Van der Linden, M., Chicherio, C., Collette, F., Degueldre, C., Franck, G., et al. (2003a) Brain correlates of performance in a free/cued recall task with semantic encoding in Alzheimer disease. Alzheimer Dis. Assoc. Disord., 17: 35–45.

Lekeu, F., Van der Linden, M., Degueldre, C., Lemaire, C., Luxen, A., Franck, G., et al. (2003b) Effects of Alzheimer's disease on the recognition of novel versus familiar words: neuropsychological and clinico-metabolic data. Neuropsychology, 17: 143–154.

Lekeu, F., Wojtasik, V., Van der Linden, M. and Salmon, E. (2002) Training early Alzheimer patients to use a mobile phone. Acta Neurol. Belg., 102: 114–121.

Leuchter, A.F., Newton, T.F., Cook, I.A., Walter, D.O., Rosenberg-Thompson, S. and Lachenbruch, P.A. (1992) Changes in brain functional connectivity in Alzheimer-type and multi-infarct dementia. Brain, 115(Pt 5): 1543–1561.

Leys, D., Steinling, M., Petit, H., Salomez, J.L., Gaudet, Y., Ovelacq, E., et al. (1989) [Alzheimer's disease: study by single photon emission tomography (Hm PAO Tc99 m)]. Rev. Neurol., 145: 443–450.

Lopez, O.L., Becker, J.T., Somsak, D., Dew, M.A. and DeKosky, S.T. (1994) Awareness of cognitive deficits and anosognosia in probable Alzheimer's disease. Eur. Neurol., 34: 277–282.

Lou, H.C., Luber, B., Crupain, M., Keenan, J.P., Nowak, M., Kjaer, T.W., et al. (2004) Parietal cortex and representation of the mental Self. Proc. Natl. Acad. Sci. USA, 101: 6827–6832.

Maguire, E.A., Frith, C.D. and Morris, R.G. (1999) The functional neuroanatomy of comprehension and memory: the importance of prior knowledge. Brain, 122(Pt 10): 1839–1850.

Maguire, E.A. and Mummery, C.J. (1999) Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus, 9: 54–61.

McDaniel, K.D., Edland, S.D. and Heyman, A. (1995) Relationship between level of insight and severity of dementia in Alzheimer disease. CERAD Clinical Investigators. Consortium to Establish a Registry for Alzheimer's Disease. Alzheimer Dis. Assoc. Disord., 9: 101–104.

McGlynn, S.M. and Schacter, D.L. (1989) Unawareness of deficits in neuropsychological syndromes. J. Clin. Exp. Neuropsychol., 11: 143–205.

Meiran, N. and Jelicic, M. (1995) Implicit memory in alzheimer's disease: a meta-analysis. Neuropsychology, 9: 291–303.

Michon, A., Deweer, B., Pillon, B., Agid, Y. and Dubois, B. (1994) Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry, 57: 805–809.

Migliorelli, R., Teson, A., Sabe, L., Petracca, G., Petracchi, M., Leiguarda, R., et al. (1995a) Anosognosia in Alzheimer's disease: a study of associated factors. J. Neuropsychiatry Clin. Neurosci., 7: 338–344.

Migliorelli, R., Teson, A., Sabe, L., Petracchi, M., Leiguarda, R. and Starkstein, S.E. (1995b) Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. Am. J. Psychiatry, 152: 37–44.

Minoshima, S., Foster, N.L. and Kuhl, D.E. (1994) Posterior cingulate cortex in Alzheimer's disease. Lancet, 344: 895.

Morris, R.G. (1994) Working memory in Alzheimer-type dementia. Neuropsychology, 8: 544–554.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology, 51: 1546–1554.

Ott, B.R., Lafleche, G., Whelihan, W.M., Buongiorno, G.W., Albert, M.S. and Fogel, B.S. (1996) Impaired awareness of deficits in Alzheimer disease. Alzheimer Dis. Assoc. Disord., 10: 68–76.

Pearson, R.C., Esiri, M.M., Hiorns, R.W., Wilcock, G.K. and Powell, T.P. (1985) Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. Proc. Natl. Acad. Sci. USA, 82: 4531–4534.

Peigneux, P., Salmon, E., Garraux, G., Laureys, S., Willems, S., Dujardin, K., et al. (2001) Neural and cognitive bases of upper limb apraxia in corticobasal degeneration. Neurology, 57: 1259–1268.

Petrides, M., Alivisatos, B., Meyer, E. and Evans, A.C. (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc. Natl. Acad. Sci. USA, 90: 878–882.

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De la Sayette, V., et al. (2003) Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. Brain, 126: 2203–2219.

Reed, B.R., Jagust, W.J. and Coulter, L. (1993) Anosognosia in Alzheimer's disease: relationships to depression cognitive function and cerebral perfusion. J. Clin. Exp. Neuropsychol., 15: 231–244.

Ruby, P. and Decety, J. (2001) Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nat. Neurosci., 4: 546–550.

Ruby, P. and Decety, J. (2003) What you believe versus what you think they believe: a neuroimaging study of conceptual perspective-taking. Eur. J. Neurosci., 17: 2475–2480.

Ruby, P. and 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: 988–999.

Salmon, D.P. (2000) Disorders of memory in Alzheimer's disease. In: Boller F. and Grafman J. (Eds.), Handbook of Neuropsychology (2nd ed.). Elsevier Science B.V., Amsterdam, pp. 155–195.

Salmon, E. (2003) Physiology of human memory explored by functional imaging. In: De Deyn P.P., Thiery E. and D'Hogge R. (Eds.), Memory. Basic Concepts, Disorders and Treatment. Acco, Leuven, pp. 321–336.

Salmon, E., Collette, F., Degueldre, C., Lemaire, C. and Franck, G. (2000) Voxel-based analysis of confounding effects of age and dementia severity on cerebral metabolism in Alzheimer's disease. Hum. Brain Mapping, 10: 39–48.

Salmon, E., Collette, F., Van der Linden, M. and Franck, G. (1999) Increased demand on executive processes decreases activity in posteromedial regions. Neuroimage, 9: S340.

Salmon, E., Garraux, G., Delbeuck, X., Collette, F., Kalbe, E., Zuendorf, G., et al. (2003) Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. Neuroimage, 20: 435–440.

Salmon, E., Lespagnard, S., Marique, P., Herhol, K., Perani, D., Holthoff, V., et al. (2005) 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., Delbeucq, X., Beuthien-Bauman, B., Pelati, O., Lespagnard, S., Collette, F. and Garraux, G. (2004). Multiple regional cerebral account for unawareness of cognitive impairment in AD. HBM Abstract, Budapest.

Salthouse, T.A. and Becker, J.T. (1998) Independent effects of Alzheimer's disease on neuropsychological functioning. Neuropsychology, 12: 242–252.

Sevush, S. (1999) Relationship between denial of memory deficit and dementia severity in Alzheimer disease. Neuropsychiatry Neuropsychol. Behav. Neurol., 12: 88–94.

Sevush, S. and Leve, N. (1993) Denial of memory deficit in Alzheimer's disease. Am. J. Psychiatry, 150: 748–751.

Squire, L.R. (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol. Rev., 99: 195–231.

Starkstein, S.E., Vazquez, S., Migliorelli, R., Teson, A., Sabe, L. and Leiguarda, R. (1995) A single-photon emission computed tomographic study of anosognosia in Alzheimer's disease. Arch. Neurol., 52: 415–420.

Tabert, M.H., Albert, S.M., Borukhova-Milov, L., Camacho, Y., Pelton, G., Liu, X., et al. (2002) Functional deficits in patients with mild cognitive impairment: prediction of AD. Neurology, 58: 758–764.

Tulving, E. (1993). Self-knowledge of an amnesic individual is represented abstractly. In: Srull, T.Kw., R.S., (Ed.) Advances in Social Cognition. Vol. 5. Erlbaum, Hillsdale, NJ, pp. 147–156.

Tulving, E. (2002) Episodic memory: from mind to brain. Annu. Rev. Psychol., 53: 1–25.

Vaidya, C.J., Gabrieli, J.D., Demb, J.B., Keane, M.M. and Wetzel, L.C. (1996) Impaired priming on the general knowledge task in amnesia. Neuropsychology, 10: 529–537.

Venneri, A. and Shanks, M.F. (2004) Belief and awareness: reflections on a case of persistent anosognosia. Neuropsychologia, 42: 230–238.

Vogeley, K., Bussfeld, P., Newen, A., Herrmann, S., Happe, F., Falkai, P., et al. (2001) Mind reading: neural mechanisms of theory of mind and self-perspective. Neuroimage, 14: 170–181.

Vogeley, K., May, M., Ritzl, A., Falkai, P., Zilles, K. and Fink, G.R. (2004) Neural correlates of first-person perspective as one constituent of human self-consciousness. J. Cogn. Neurosci., 16: 817–827.

Weinberger, D.R. (1993) A connectionist approach to the prefrontal cortex. J. Neuropsychiatry Clin. Neurosci., 5: 241–253.

Wheeler, M.A., Stuss, D.T. and Tulving, E. (1997) Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. Psychol. Bull., 121: 331–354.

Wicker, B., Ruby, P., Royet, J.P. and Fonlupt, P. (2003) A relation between rest and the self in the brain? Brain Res. Brain Res. Rev., 43: 224–230.

Yonelinas, A.P. and Jacoby, L.L. (1995) Dissociating automatic and controlled processes in a memory-search task: beyond implicit memory. Psychol. Res., 57: 156–165.

Zanetti, O., Vallotti, B., Frisoni, G.B., Geroldi, C., Bianchetti, A., Pasqualetti, P., et al. (1999) Insight in dementia: when does it occur? Evidence for a nonlinear relationship between insight and cognitive status. J. Gerontol. B Psychol. Sci. Soc. Sci., 54: 100–106.