Voxel-Based Analysis of Confounding Effects of Age and Dementia Severity on Cerebral Metabolism in Alzheimer's Disease

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Abstract: Alzheimer's disease is characterized by early hippocampal lesions, but neuropathological and functional imaging studies have also demonstrated involvement of associative cortices in patients suffering from this illness. New image-processing technologies have led to demonstration of predominant posteromedial cortical metabolic impairment in the disease. Confounding effects of both age and dementia severity on brain metabolism were assessed using categorical and correlational analyses performed with Statistical Parametric Mapping. Posterior cingulate and precuneus metabolism, assessed by positron emission tomography, was significantly correlated with age in a population of 46 patients with probable Alzheimer's disease. Metabolism in posterior cingulate and precuneus was higher in elderly than in younger patients with a diagnosis of Alzheimer's disease, even when dementia severity was taken as a confounding covariate. The data suggest that the sensitivity of positron emission tomography for the diagnosis of Alzheimer's disease is reduced in elderly cases, where less severe pathology is sufficient to induce clinical symptoms of dementia. Conversely, higher posteromedial metabolic impairment in early onset cases may reflect greater density of regional cerebral lesions or major decrease of functional afferences in a richly connected multimodal associative area. Posterior cingulate metabolism was also correlated to dementia severity, even when age was taken as a confounding covariate, whereas metabolism in the hippocampal formation was not shown to correlate with global cognitive deficit. Functional correlation was maintained between posterior cingulate and middle frontal cortex in demented patients as in elderly controls. The key role of posteromedial cortex in cognitive dysfunction assessed in Alzheimer's disease is probably related to its highly integrated position within attentional, visuospatial and memory neuronal networks. *Hum. Brain Mapping* 10:39–48, 2000. © 2000 Wiley-Liss, Inc.

Key words: PET; dementia; age; cingulate; precuneus

INTRODUCTION

Alzheimer's disease (AD) is heterogeneous from a clinical and genetic viewpoint, concerning age at onset of first symptoms or according to importance of cerebral biochemical and metabolic abnormalities. Heterogeneity is also observed in clinical evolution and in response to therapeutic strategies.

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Decrease of global brain metabolism has been reported in AD, and in spite of metabolic heterogeneity, a characteristic pattern was frequently described where associative posterior and frontal regions were predominantly involved whereas primary cortices and subcortical structures were relatively spared [Fazio et al., 1992; Frackowiak et al., 1981; Kuhl et al., 1985; Waldemar et al., 1994]. New image-processing and statistical programs allowing voxel-by-voxel analysis of cerebral metabolism have been validated in AD [Kennedy et al., 1995; Minoshima et al., 1995; Signorini et al., 1999]. Such programs have revealed that most significant decrease of metabolism in AD populations and even in very early cases or in at risk subjects occurs in posteromedial cortex [Minoshima et al., 1994, 1997; Reiman et al., 1996; Salmon et al., 1997].

Heterogeneity in AD has allowed to study relationships between regional cerebral metabolism and behavioural performances [Grady et al., 1988; Haxby et al., 1985; Perani et al., 1993] and voxel-based methods of analysis have already been used to study clinico-metabolic and interregional functional relationships [Collette et al., 1997; Desgranges et al., 1998; Mentis et al., 1995]. Previous reports (using mainly regions-of-interest) showed that confounding covariables such as dementia severity and age may interfere with those correlational analyses in AD [Frackowiak et al., 1981; Haxby et al., 1988; Ichimiya et al., 1994; Mann et al., 1992; Mielke et al., 1991; Minoshima et al., 1997; Small et al., 1989]. The present study was planned to carefully reassess the relative influence of both variables in metabolic studies analysed with voxel-based programs.

MATERIAL AND METHODS

Populations

Forty-six patients with a diagnosis of probable Alzheimer's disease were selected according to both DSM IV and NINCDS-ADRDA criteria [APA, 1994; McKhann et al., 1984]. The population of patients comprised 24 subjects with early onset and 22 patients with late onset dementia (using a cut-off age at onset of 65 years). The two groups were significantly different as concerns age at examination (62.7 ± 6.7 years vs. 73.3 ± 4.3 years, $P < 0.001$) and score on Mini Mental State Exam or MMSE [Folstein et al., 1975]. Mean MMSE score was 15.8 ± 6.4 in early onset AD, and 20.9 ± 5.1 in late onset AD, so that MMSE score was introduced as a confounding covariate when studying the influence of age on brain metabolism in AD. Subgroups of patients with similar dementia se-

verity were also used for categorical brain metabolic analyses. Disease duration was not significantly different between groups (3.4 ± 2.5 vs. 2.3 ± 1.1 years). Male/female ratios were 11/13 and 13/9 in early onset and late onset AD, respectively, and absence of gender differences in metabolic activity of AD patients was previously reported [Minoshima et al., 1997]. The relationship between age and MMSE score at examination was nearly significant in the AD population ($P < 0.07$). Age was subsequently taken as a confounding covariate when dementia severity was correlated to cerebral metabolism. Before analysing the AD population, a categorical comparison was performed between patient and control data, to confirm previous reports [Kennedy et al., 1995; Minoshima et al., 1994]. Brain metabolism was obtained from 11 carefully selected healthy controls, with neither previous medical history, neurological symptoms nor any medication. Mean age in control population was 58.9 ± 9.4 years. It was not significantly different from that in early onset AD patients, but age difference with the entire AD group was significant (67.7 ± 7.7 years, $P < 0.05$). Age was taken as a confounding covariate in that preliminary categorical comparison, because of its known effect on normal brain metabolic distribution [Garraux et al., 1999; Martin et al., 1991].

Methods

Scans were obtained in all subjects during quiet wakefulness with eyes closed, on a Siemens 951/31R tomograph (CTI, Knoxville, TN, USA), with collimated septa extended, using (18F)fluorodeoxyglucose, as previously published [Salmon et al., 1997]. The protocol was approved by the Ethic Committee of the University of Liège and all subjects and relatives gave informed consent. Subjects were fasted for at least 3 h prior to scanning. A transmission scan was acquired for attenuation correction using three rotating sources of ^{68}Ge . Seven millicuries of (18F)fluorodeoxyglucose were injected intravenously, and transaxial images acquisition (20 min duration) was started 30 min following the injection. Emission scans were reconstructed using a Hanning filter at a cut-off frequency of 0.5 Hz, giving a transaxial resolution of 8.7 mm full width at half maximum (FWHM), and an axial resolution of 5 mm FWHM for each of 31 planes, with a total field of view of 10.8 cm in the axial direction.

Data analysis

PET scans were analysed by using statistical parametric mapping (SPM 96, Wellcome Department of

Cognitive Neurology, London, U.K.) [Friston et al., 1995; Signorini et al., 1999], in Matlab (Math Works, Natick, MA, USA). For each scan, the 31 transverse planes were interpolated to 43 planes to render the voxels approximately cubic. Images were subsequently normalised into Montreal Neurological Institute (MNI) space, with reference to the standard stereotactic anatomical Talairach space [Talairach and Tournoux, 1988], and were smoothed using a Gaussian filter (12 mm FWHM) both to accommodate inter-subject differences in gyral and functional anatomy and to increase the signal-to-noise ratio in the dataset. Images were individually checked to detect normalisation problems (only one scan had to be removed from the initial 47 scan series). Due to slight differences in head positioning, effective “field-of-view” for this study covered planes located at –28 mm from the AC-PC line to 50 mm above this reference plane. Differences in global metabolism between all subjects were removed using proportional scaling, on a voxel-by-voxel basis. For each voxel in the stereotactic space, the program generated an adjusted mean value of cerebral metabolic rate of glucose and an associated adjusted error variance. In the categorical comparisons (AD patients vs. controls and early vs. late onset AD), significant differences between groups were estimated on a voxel-by-voxel basis using the *t* statistic. The resulting set of *t* values constituted the statistical parametric map SPM(*t*) [Friston et al., 1991]. The SPM(*t*) was then transformed to the unit normal distribution to give a SPM(*Z*). Correlations between clinical and metabolic variables were computed on a voxel-by-voxel basis by covariance analysis, using appropriate parameters as confounding covariates (see

TABLE I. Significant decreases of metabolism in Alzheimer’s disease

	x	y	z	Z
Posterior cingulate	4	–46	24	4.8
(BA 23/31) ^a	–8	–50	24	4.5
	0	–38	28	4.4

^a BA, Brodmann’s area. Coordinates (x,y,z) refer to a standard stereotactical space (Talairach and Tournoux, 1988). SPM is thresholded to $P < 0.001$.

Results). For both types of analysis, we first used a SPM with a Z score threshold of 3.09 ($P < 0.001$). Decrease of metabolism or correlation was then characterised in terms of the probability that the metabolic variation could have occurred by chance over the entire volume analysed (corrected P value < 0.05). SPM with a Z score threshold of 2.33 ($P < 0.01$) was further used for testing a priori hypotheses on regional metabolic variation. Coordinates of brain regions in text and tables refer to the stereotactical space of reference.

RESULTS

Categorical comparison: AD versus control population

In a confirmatory analysis, the entire population of AD patients was compared with the control group. A significant decrease of metabolism was confirmed in posterior cingulate cortex (BA 23/31; Table I and Fig. 1) and metabolic impairment was not confounded by

Figure 1.

Statistical parametric map ($P < 0.001$) showing significant decrease of metabolism in posterior cingulate cortex in patients with Alzheimer’s disease compared to a control population.

age. Involvement of lateral and temporal associative cortices was only observed with lower statistical threshold [Salmon et al., 1997]. The inverse subtraction showed a classical pattern of relatively preserved metabolism in AD compared to controls, in cerebellum ($-4, -58, -24; Z = 7.12$), postcentral lobule (BA 5; $12, -28, 48; Z = 6.39$), precentral gyrus (BA 4/6; $-52, -8, 24; Z = 5.83$), ventro-postero-lateral nucleus of thalamus ($18, -18, 4; Z = 5.12$), and putamen ($26, 4, 4; Z = 4.57$).

Categorical comparison: early and late onset AD groups

The population of patients was then divided into early ($n = 24$) and late onset ($n = 22$) groups, taking 65 years as cut-off age at onset. When compared to controls (without confounding covariate), the early onset group showed significant hypometabolism in BA 31 ($-2, -56, 24; Z = 5.97$) and precuneus ($22, -72, 28; Z = 4.56$). In the late onset group, the SPM threshold had to be decreased to $P < 0.01$ to observe significant hypometabolism, which was observed in BA 23 ($2, -44, 24; Z = 3.99$). When both groups were compared directly, cerebral glucose metabolism was relatively lower in early than in late onset AD patients in posterior cingulate (BA 31; $-4, -58, 24; Z = 4.54$) and precuneus (BA 31; $-18, -66, 20; Z = 3.96$).

Metabolic differences between early and late onset AD groups persisted ($P < 0.01$) when individual MMSE scores were taken as confounding covariates. To further control for possible confounding effect of dementia severity, 15 patients with matched MMSE scores were selected from both the early onset and the late onset groups. Mean age was 61.3 ± 7.9 and 72.8 ± 4.7 , and mean MMSE scores were 19.5 ± 5.1 and 19.7 ± 4.9 , respectively. SPM (thresholded at $P < 0.01$) confirmed that younger AD subjects had significantly lower posterior cingulate metabolism than elderly AD patients.

Correlational study: age and brain metabolism in AD

To avoid arbitrary categorisation of the AD population according to a cut-off age, the correlation between age and metabolism was studied, with or without use of dementia severity as confounding covariate. A significant correlation between age at disease onset and metabolism was observed in posterior cingulate/precuneus (BA31; $6, -58, 28; Z = 3.98$) in the AD population. This correlation was maintained when MMSE score was taken as a confounding covariate, or

Figure 2.

Illustration of the significant correlation obtained between age and metabolism in posterior cingulate region in Alzheimer's disease but not in controls.

when patients with matched dementia severity from early and late onset groups ($n = 30$) were considered.

Age at PET examination was used in a confirmatory "voxel-of-interest" analysis to compare AD patients and controls, using adjusted metabolic values in BA31. The correlation between age and posterior cingulate metabolic values was clearly greater in our AD population than in healthy elderly volunteers (Fig. 2).

Correlational study: dementia severity and brain metabolism in AD

A significant correlation between MMSE score and regional brain metabolism in Alzheimer's disease was observed in posterior cingulate and precuneus, and in the left precentral cortex (BA 6; Table II and Fig. 3). Figure 4 shows individual values, illustrating the cor-

TABLE II. Correlation between dementia severity and metabolism in Alzheimer's disease

	x	y	z	Z
Posterior cingulate (BA 31) ^a	0	-56	28	4.1
Precuneus (BA 7)	14	-74	36	3.9
Left precentral gyrus (BA 6)	-36	0	36	3.7

^a BA, Brodmann's area. Coordinates (x,y,z) refer to a standard stereotactical space [Talairach and Tournoux, 1988]. SPM is thresholded to $P < 0.001$.

Figure 3.

Statistical parametric map ($P < 0.001$) showing the correlation between dementia severity and metabolism in posterior cingulate and premotor cortices of Alzheimer patients.

relation between MMSE score and metabolism in posterior cingulate in AD. Activity in the hippocampal formation was not shown to correlate with MMSE score in this SPM analysis. The range of MMSE scores in elderly controls (27 to 30) was too narrow to allow correlation.

Interregional correlations (functional correlations)

Finally, interregional correlation analysis was performed between voxel showing the most significant

hypometabolism in AD (first voxel in Table I) and whole brain metabolism, using a SPM thresholded at $P < 0.01$ (Fig. 5). Posterior cingulate metabolism was significantly correlated with activity in right frontal cortex (centred on BA 6/8; 30, 4, 52; $Z = 3.65$), and left frontal cortex (centred on BA 6/8; coordinates $-28, 10, 48$; $Z = 3.06$). We also report a metabolic correlation between posterior cingulate and left middle temporal gyrus (centred on BA 21; coordinates $-54, -32, -12$; $Z = 3.57$). Results were similar when first voxel in Table II was used. There was no significant difference in correlations between AD patients and controls.

Figure 4.

Illustration of the significant correlation obtained between dementia severity (score on mini mental state examination) and metabolism in posterior cingulate region in Alzheimer's disease.

DISCUSSION

Comparison of brain metabolism between our groups of patients and controls only aimed at confirming that posterior cingulate metabolism was most significantly reduced in a large AD population, using new data analysis program that allowed exploration of whole brain metabolic variations on a voxel-by-voxel basis [Friston et al., 1995; Kennedy et al., 1995; Signorini et al., 1999]. The predominance of posterior cingulate hypometabolism in AD has rarely been emphasized when regions-of-interest were used for data analysis [Fazio et al., 1992; Nyback et al., 1991]. Advantages of voxel-based analyses have already been emphasized in AD [Signorini et al., 1999]. Metabolic (or cerebral blood flow) reduction was observed in posterior cingulate cortex, medial parietal, parieto-temporal and frontal neocortex [Ishii et al., 1997; Minoshima et al., 1994, 1997; Reiman et al., 1996], even in subjects at risk for AD [Reiman et al., 1996]. Medial posterior cortices (posterior cingulate and precuneus)

Figure 5.

Statistical parametric map ($P < 0.01$) showing that middle frontal metabolism is significantly correlated with that in posterior cingulate.

were most significantly involved when global metabolism effect was removed by proportional scaling, whereas middle temporal or lateral parietal metabolic impairment could only be demonstrated by lowering the significance level [Salmon et al., 1997].

Metabolism in medial temporal areas was not significantly decreased in our AD population, nor was it related to age at onset or to dementia severity. Metabolic involvement of medial temporal regions in AD is quite variable among studies in the literature [Cutler et al., 1985; Fazio et al., 1992; Minoshima et al., 1997; Vander Borgh et al., 1997]. More significant medial temporal hypometabolism observed with regions-of-interest analysis in AD might be related to partial volume effect due to well-described regional atrophy [Meltzer et al., 1996; Slansky et al., 1995].

Possible causes of posterior cingulate hypometabolism in AD: regional atrophy

Neuropathological staging of AD-related changes has been characterised by initial lesions in the transentorhinal region, followed by involvement of hippocampus, amygdala, and magnocellular forebrain nuclei [Braak and Braak, 1991]. The retrosplenial region is among the first isocortices affected in AD [Braak and Braak, 1991], and besides medial temporal limbic areas, the posterior cingulate gyrus and the superior parietal lobule showed the most severe neuropathological degeneration in a number of AD cases in the literature [Brun and Englund, 1981]. However, neuronal loss is most variable in posterior cingulate cortex [Brun and Englund, 1981], and the laminar distribution of neuronal degeneration in this region is

also variable between AD patients [Vogt et al., 1990]. We did not perform voxel-by-voxel atrophy correction of our metabolic data. Previous studies have shown that brain metabolic differences between healthy controls and AD patients remain significant following correction for partial volume effect because of brain atrophy, but they are proportionally smaller [Alavi et al., 1993; Labbé et al., 1996; Meltzer et al., 1996]. A similar conclusion was drawn for the predominant posterior cingulate hypometabolism observed in AD populations [Ibanez et al., 1998]. Confounding effect of cerebral metabolic abnormalities and regional brain atrophy would be best studied in future research by separate analysis of functional and anatomical data using voxel-based methods.

Possible causes of posterior cingulate hypometabolism in AD: functional deafferentation

The intense metabolic dysfunction observed in posterior cingulate probably corresponds to functional deafferentation in a richly connected multimodal associative area, in agreement with the hypothesis of interregional disconnection in Alzheimer's disease [Pearson et al., 1985]. In the literature, posterior cingulate has been shown to be connected to posterior parietal areas, anterior cingulate, parahippocampal and hippocampal, superior temporal, lateral and orbito-frontal cortex and thalamic limbic nuclei. Consistent with this, our interregional correlations emphasized a significant relationship between metabolism in posterior cingulate gyrus (and precuneus) and posterior middle frontal cortex. Those connections explain why posterior cingulate has been considered to be an

interface area between the neocortex and the limbic system [Baleydier and Mauguier, 1980, 1985; Vogt and Pandya, 1987]. Our interregional metabolic correlations show that posterior cingulate cortices remain functionally related to middle frontal and lateral temporal regions, and lowered activity in posteromedial multimodal associative regions could depend on decreased basal activity from those different regions.

Clinico-metabolic relationships in AD

A main point of interest of this report was to reassess previously described relationships between brain metabolism and important clinical variables in Alzheimer's disease: the relative (and possibly confounding) effects of age and dementia severity were specifically studied. Gender was reported not to affect metabolic impairment in AD [Minoshima et al., 1997]. Other confounding variables, such as education or premorbid intellectual ability [Alexander et al., 1997] or apolipoprotein E genotype [Reiman et al., 1996] could influence differential brain metabolic distribution between controls and at risk subjects. On the other hand, white matter abnormalities could significantly influence regional brain metabolism [DeCarli et al., 1996], but our patients had no significant vascular risk factors and there were no density lowering on CT scans. Voxel-based analyses allowed to study clinico-metabolic correlations without a priori hypotheses, and high statistical levels were chosen to emphasize most significant relationships.

Relationship between age and brain metabolism in AD

Several functional imaging studies have previously shown lower activity in associative cortices of early, compared to late onset, AD patients. In some (but not all) reports, the difference between senile and presenile cases disappeared when disease severity was taken into account [Habert et al., 1991; Ichimiya et al., 1994; Mielke et al., 1991; O'Brien et al., 1992; Small et al., 1989]. On the other hand, voxel-based programs have already been used to study relationship between age and metabolism (or cerebral blood flow) in control populations, and a decrease of activity was observed with ageing in frontal and anterior cingulate cortices, and in perisylvian areas [Garraux et al., 1999; Martin et al., 1991; Petit-Taboué et al., 1998]. Metabolic decrease in precuneus and posterior cingulate was more significant in our early onset than our late onset AD group, even when differences in dementia severity were taken into account. Moreover, there was a significant correlation between age and pos-

terior cingulate metabolism of AD patients, demonstrating a gradual, rather than a categorical relationship. This correlation was also maintained in AD when MMSE score was taken as a confounding variable, and it was not observed in controls, as expected from previous reports. Neuropathological studies have already demonstrated a strong negative correlation between age at onset of AD and degeneration in frontal, temporal and parietal areas, which are all richly interconnected with posterior cingulate [Hansen et al., 1988]. Levels of choline-acetyltransferase in AD were positively correlated with advancing age in associative regions [Hansen et al., 1988]. Although neuropathological lesions are not always graded in AD [Vogt et al., 1990], they are frequently of greater severity in early onset patients. The lesions in different brain areas probably contribute through functional deafferentation to a graded precuneus/posterior cingulate hypometabolism that is more severe in younger AD patients. A positive relationship has been repeatedly observed between age and a metabolic ratio comparing metabolism in associative cortices to that in relatively spared primary cortices and subcortical regions in AD [Herholz et al., 1993; Mielke et al., 1991]. The reason for this type of difference between metabolic (and neuropathological) abnormalities in early and late onset AD patients is not clear. However, the fact that dementia is diagnosed in elderly patients when their metabolic level is significantly higher than that of younger AD subjects is compatible with the observation that age constitutes a risk factor for the disease. Conversely, data obtained in relatively young, cognitively unimpaired subjects at risk for Alzheimer's disease confirm that metabolic activity is already low in associative areas before onset of clinical symptoms in this population [Kennedy et al., 1995; Reiman et al., 1996]. This suggests that a mechanism of cognitive compensation may influence the expression of dementia [Alexander et al., 1997].

SPM analysis showed no relationship between parahippocampal metabolism and age in AD patients. Accordingly, there was no difference between the neuropathological lesions observed in hippocampal formation in early and late onset AD [Hansen et al., 1988].

Relationship between dementia severity and brain metabolism in AD

MMSE scores in our AD population were significantly correlated with glucose metabolism in precuneus/posterior cingulate and in posterior middle frontal cortex, even when factoring out the effect of age. Dementia severity has previously been correlated with whole brain metabolism in AD [Alavi et al., 1993] and

with middle frontal and temporo-parietal metabolism [Haxby et al., 1988; Ichimiya et al., 1994; Mielke et al., 1991; Salmon et al., 1996]. It was also related to frontal metabolic involvement [Frackowiak et al., 1981; Haxby et al., 1988; Mann et al., 1992]. Our data obtained with SPM method confirm the relationship reported between MMSE scores and posterior cingulate metabolism in AD using 3D-SSP, another voxel-based program of analysis [Minoshima et al., 1997].

Correlation with posterior cingulate metabolism is not a universal, nonspecific feature in AD, for several memory scores were correlated with metabolism in other brain areas when SPM was used without a priori hypothesis [Collette et al., 1997; Desgranges et al., 1998]. MMSE score is a composite of various cognitive performances, and we also observed a relationship between posterior cingulate metabolism and score at Mattis dementia rating scale [Collette et al., 1998]. The progression of Alzheimer's disease is frequently assessed by composite neuropsychological scores, which comprise performances on different tasks that are subserved by associative cortices [Folstein et al., 1975; Mattis, 1976; Welsh et al., 1992]. Our interregional correlations showed a significant relationship between metabolic activity in posterior cingulate/precuneus and in posterior middle frontal cortex. The important functional connections between posterior cingulate area, temporo-parietal and frontal cortices probably explain why the metabolic level in those regions was frequently related to a global score of dementia severity. Metabolic impairment in posterior cingulate and precuneus is certainly a major characteristic of Alzheimer's disease. A posteromedial metabolic decrease was also observed over a mean duration of 18 months in another population of fifteen AD patients whose mean MMSE score decreased from 21 to 16 (unpublished observation).

Functional significance of posteromedial hypometabolism

The organisation of posteromedial regions is poorly understood, and functional imaging studies demonstrate considerable variability in the relative activation patterns of posterior cingulate and precuneus [Fletcher et al., 1995]. Precuneus is a multimodal sensory associative area that is intimately connected with posterior cingulate [Baleydier and Mauguire, 1980]. Both regions are involved in a large scale network subserving visuospatial directed attention [Mesulam, 1990]. Precuneus was activated in several tasks of directed attention studied with PET [Corbetta et al., 1993; O'Leary et al., 1997; Vandenberghe et al., 1996]. It has been suggested that

posteromedial regions allow conscious evaluation of the (external) environment [Vogt et al., 1992]. However, they are also activated when subjects mentally perform spatial orientation tasks [Maguire and Frith, 1997], implying that they are involved in processing of "internal" as well as afferent "external" information. In keeping with the hypothesis of conscious evaluation of the environment, it is noteworthy that posterior cingulate and precuneus activity was decreased during sleep, when compared to wakefulness [Maquet et al., 1996, 1997].

On the other hand, posterior cingulate is clearly involved in a general memory network, as its metabolism is decreased in global amnesia [Fazio et al., 1992]. Further, retrosplenial amnesia has previously been described [Valenstein et al., 1987]. Posterior cingulate and/or precuneus were activated in numerous memory tasks that explored the neural substrate of episodic memory [Fletcher et al., 1995; Petrides et al., 1993a, 1995], and working memory [Owen et al., 1996; Petrides et al., 1993b; Smith et al., 1996]. The complex role of posterior medial cortices has not been fully characterised, but they occupy a key position between limbic and associative areas [Baleydier and Mauguire, 1985]. All these data suggest that posteromedial regions probably play a major role in the interaction and integration of several cognitive processes and between several functional networks in the human brain. Progressive deficits in interactions between these specific networks, related to progressive metabolic decrease in posterior cingulate and precuneus, would appear to contribute to the worsening of dementia in Alzheimer's disease.

In conclusion, both age at onset and dementia severity were significantly correlated to metabolic impairment in posteromedial cortices of patients with Alzheimer's disease. Lower activity in posterior cingulate and precuneus in AD patients might reflect high regional lesion density or important loss of functional afferences in a richly connected multimodal associative area. Preserved functional correlation between posterior cingulate and other associative cortices known to be metabolically impaired in AD (middle frontal and lateral temporal regions) is in agreement with the later hypothesis. Combined correlational studies of clinical variables with both functional and anatomical data analysed with voxel-based method in AD patients could help to disentangle confounding influences of atrophy and functional deafferentation.

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