CHAPTER 34

Brain Imaging in Prodromal and Probable Alzheimer's Disease. A Focus on the Cingulate Gyrus

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Chapter contents

Brain imaging in Alzheimer's disease (AD) has greatly benefited from technological advances. Shifting from computed tomography (CT) to magnetic resonance imaging (MRI) allowed progress from linear to volumetric measurements of brain atrophy (Frisoni *et al.*, 2003). Pioneer functional imaging work with low-resolution positron emission tomography (PET) machines and a method using *a priori* selected regions-of-interest (ROI) almost anecdotally reported posterior cingulate cortex involvement in AD, among several other associative cortices (Cutler *et al.*, 1985). However, voxel-based analyses of the entire brain metabolism much more convincingly demonstrated a wide metabolic impairment in the posteromedial cortex, comprising posterior cingulate and medial parietal (precuneus) cortices (Minoshima *et al.*, 1994). Voxel-based analyses allowed the comparison of cerebral images between populations and the search for clinico-metabolic comparisons without any *a priori* anatomical hypothesis. Emerging techniques offer the possibility to measure decreased posterior cingulate biological brain components in AD with proton MR spectroscopy (Hattori *et al.*, 2002; Mielke *et al.*, 2001), but we lack correlations with neuropathology to correctly interpret the data. Diffusion tensor imaging (DTI) provides a technique for the assessment of the integrity or disorganization of white matter tracts, in the temporal subcortical white matter, the cingulum bundle, and the corpus callosum, for example (Takahashi *et al.*, 2002). The technique is still

in development, but some purposes have already been achieved as DTI abnormalities in posterior cingulate white matter were shown to correlate with disease severity in AD (Yoshiura *et al.*, 2002).

Data have now been gathered on large populations of patients, in which posterior cingulate, temporoparietal, and prefrontal associative cortices were consistently affected (Herholz *et al.*, 2002), but pathological confirmation of AD diagnosis was obtained in only few studies (Silverman *et al.*, 2001). Then, the exact sensitivity, specificity, and positive predictive value of posterior cingulate and lateral associative cortices hypometabolism for the diagnosis of AD remains questioned. There is now a major interest in studying patients in the very early stages of AD. Patients with mild cognitive impairment (MCI) are able to perform usual activities of daily living but they suffer isolated difficulties with memory, attention, or executive functions exceeding those expected on the basis of aging (Petersen *et al.*, 1999; DeCarli, 2003; Chapter 33). Studies have demonstrated that MCI patients are at risk for developing AD and those subjects were called 'questionable AD' (Hughes *et al.*, 1982); however, some patients will never convert and might even show clinical improvement. Consequently, only longitudinal studies can provide *a posteriori* selection of patients with prodromal AD, when conversion to dementia occurs, and pathological verification of probable AD will still require a longer delay. This categorization is of utmost importance, for the pathophysiology of 'non-converters' MCI is probably heterogeneous and different from AD, and their medial temporal or cingulate cortex involvement might not be in the foreground (Anchisi *et al.*, 2005).

Two main pathological poles emerged from the available neuroimaging data reported in AD. On the one hand, structural imaging focused on an early medial temporal involvement, in a context of global atrophy (Chetelat & Baron, 2003; Poulin & Zakzanis, 2002); however, posterior cingulate atrophy was also reported (Callen *et al.*, 2001; Fox *et al.*, 2001). On the other hand, functional imaging showed early posterior cingulate and lateral temporoparietal involvement, probably accompanied by a disconnection between frontal and posterior associative cortices (Nestor *et al.*, 2003a; Salmon *et al.*, 2000), but initial medial temporal hypoperfusion was also described. The two poles have complex and different functional roles, they were specifically related to different measures of memory impairment in AD, but their relative contribution to the predominant amnesic syndrome in the disease remains a matter of debate (Desgranges *et al.*, 2002; Lekeu *et al.*, 2003b).

One important caveat is that currently available voxel-based methods of analysis are designed for group studies more than for individual analysis. Most structural measures are not of high predictive value in an individual case, and more studies are required to determine the accuracy of decreased medial posterior activity in predicting evolution of individual MCI patients to probable or definite AD and even in characterizing individual AD patients (Kaneko *et al.*, 2004; Wolf *et al.*, 2003; Herholz *et al.*, 2002). Moreover, most statistical analyses reported in the literature were univariate (comparisons were made separately at each voxel or ROI level), whereas multivariate analyses may better explain how ensembles of brain regions are modified by AD (Sackeim *et al.*, 1993). For example, principal component analysis (PCA) of entire three-dimensional images (Zuendorf *et al.*, 2003) may better highlight heterogeneity in MCI and AD (Grady *et al.*, 1990; Scarmeas *et al.*, 2004). We will show that AD cannot be restricted to a linearly progressing disease. AD is a multivariate pathology, with different dysfunctional poles and a pivotal cingulate involvement (Salmon *et al.*, 2007a).

Goals of This Chapter

This chapter will provide an overview of the available information on structural and functional brain imaging in AD, the main pathological poles will be described and the multivariate nature of the disease will be highlighted. We will particularly concentrate on the cingulate cortex, trying to understand the clinical consequences of damage in the posterior and anterior parts of this structure. Specific topics that will be successively addressed include:

1 Structural imaging abnormalities at early stages of AD, mainly in the hippocampus, but also beyond medial temporal structures.

2 Unity and diversity of brain metabolic impairments in probable AD; arguments for a multivariate pathology.

3 Functional data available on groups of prodromal AD.

4 Clinical correlates of impaired posterior cingulate metabolism in AD: episodic and autobiographical memory.

5 Clinical correlates of impaired anterior cingulate metabolism in AD: behavioral symptoms.

6 Complex interaction between metabolism and genotype.

7 Multiple functional imaging opportunities: adding diversity in AD.

Conclusion: AD is characterized by variable functional involvement of selective pathological poles, and the relative 'weight' of regional functional impairment is related to clinical symptoms.

Structural Imaging

Linear measurements of brain atrophy were essentially focused on medial temporal pathology, and the cingulate cortex was not investigated (Frisoni *et al.*, 2003). Whole brain assessment with voxel-based morphometry of MRI images, however, did not depend on *a priori* anatomical hypotheses restricted to the hippocampus and showed gray matter loss not only in the medial temporal structures, but also in the posterior cingulate gyrus, the precuneus cortex, and the temporoparietal association cortices in early AD (Baron *et al.*, 2001; Frisoni *et al.*, 2002). Gray matter loss was reported in posterior and anterior cingulate areas in another study on early AD (Miller *et al.*, 2003). Progressive atrophy was revealed in presymptomatic individuals with a familial history of AD who eventually became demented, and posterior cingulate, neocortical temporoparietal and medial temporal regions were all involved in the presymptomatic stage (Fox *et al.*, 2001). Thus, posterior cingulate cortex atrophy appears in mild stages of AD and even in asymptomatic subjects with familial AD.

In groups of amnesic MCI patients, voxel-based morphometry showed atrophy in hippocampus, posterior cingulate, and the subcallosal anterior cingulate cortex (ACC) (Chetelat *et al.*, 2002). More precisely, baseline-MRI measures of the entorhinal cortex, the banks of the superior temporal sulcus, and the ACC were most useful in discriminating the status of MCI subjects (conversion or not to AD) on follow-up examination (Killiany *et al.*, 2000). In summary, voxel-based measurements assessing brain atrophy in the entire brain volume of AD patients more frequently pointed to medial temporal pathology than to cingulate involvement (Karas *et al.*, 2004). There is a lack of information concerning the clinical consequences of cingulate atrophy in structural neuroimaging studies. Moreover, the sensitivity and specificity of structural measures appear relatively disappointing at an individual patient level.

Functional Imaging in Probable and Definite AD

In early stages of AD, some authors suggest that hypoperfusion predominates in medial temporal regions, where it subsequently reaches a plateau (Nebu *et al.*, 2001). When single-photon emission computerized tomography (SPECT) perfusion images were obtained in subjects who subsequently died and were classified according to 'Braak staging' for AD, reduced activity between the 'entorhinal' and the 'limbic' stages appeared in the anterior part of the medial temporal lobe, subcallosal area, posterior cingulate, and precuneus cortices (Bradley *et al.*, 2002). In most studies, however, activity in the posterior cingulate gyrus, the precuneus cortex, and in lateral temporoparietal- and frontal associative cortices decreases with the severity of dementia and this reduction appears more important than impaired hippocampal activity even in mild dementia stages (Hirono *et al.*, 2004; Matsuda *et al.*, 2002). This provides the typical pattern reported in probable AD populations. A major concern is that the magnitude and the sequence of longitudinal brain functional changes are likely to vary between different AD patients. Accordingly, selective impairment of declarative memory in a subgroup of patients was associated with hypoperfusion in bilateral mesial temporal regions of interest, while posterior associative cortices were predominantly involved in AD subjects with more widespread cognitive impairment (Cappa *et al.*, 2001). Although Braak staging of AD cannot be rejected by available univariate analyses of functional imaging, a single linear evolution of the disease is not sufficient to explain the important heterogeneity in the data. Effectively, (1) there is a variable involvement of medial temporal structures and posterior associative cortical areas, related to variable clinical characteristics, (2) subgenual and posterior cingulate cortices are damaged early in a number of AD samples studied so far, and (3) the activity in posterior cingulate and posterior associative cortices (but not in hippocampal structures) generally decreases with increasing severity of dementia (Herholz *et al.*, 2002; Salmon *et al.*, 2007a). Noteworthy, there are also reports of frontal variant AD in the functional imaging literature that do not fit a unique scheme of 'Braak progression' (Salmon *et al.*, 1994; Mann *et al.*, 1992).

Clinicians do accept that episodic memory impairment is the most frequent presenting symptom in AD (McKhann *et al*, 1984), but they have always recognized different clinical 'subgroups' in AD patients (Cappa *et al.*, 2001). There are trends for both unity and diversity of physiopathology in all domains of AD research, and those trends are not mutually exclusive. Accordingly, an inverse correlation was observed between posterior cingulate activity and age of AD patients, even when dementia severity was taken into account (Salmon *et al.*, 2000). The data suggest that posterior cingulate cortex is a major target for AD pathology in 'young' patients, but that brain metabolic impairment is much more distributed in elderly patients (Fig. 34.1). In the same vein, posterior cingulate hypometabolism is more important in early onset than in late onset AD (Sakamoto *et al.*, 2002). Moreover, the decrease of posterior cingulate and medial temporal activity is greater in familial than in sporadic forms of AD (Mosconi *et al.*, 2003). In summary, there is a characteristic 'general' pattern of metabolic impairment in

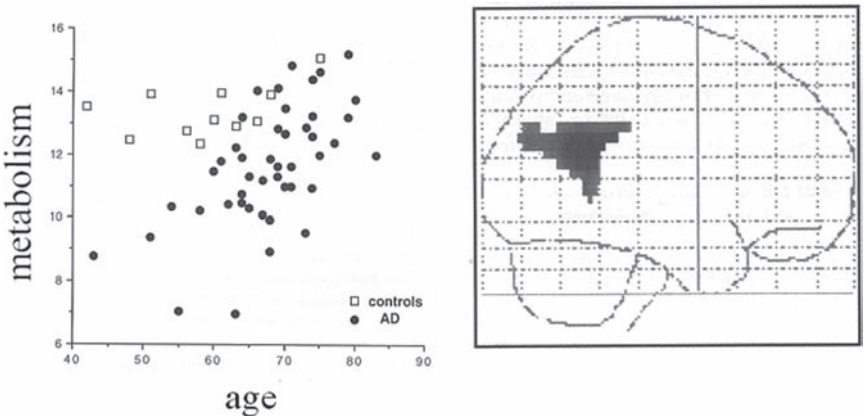

Fig. 34.1 Lateral projection on a 'glass-brain' representation of posterior cingulate metabolic impairment observed in AD patients compared with elderly controls. The decrease of metabolism is linearly correlated with age in AD (but not in controls), and posterior cingulate involvement is quite variable in the elderly patients.

probable and definite AD, with predominant posterior cingulate, precuneus, and associate lateral temporal, parietal and premotor involvement, but a non-negligible variability does exist, related to many factors such as dementia stage, age, education, genetics, and clinical symptoms, for example. This is in keeping with the idea that AD is a multivariate pathology.

Multivariate analyses of brain metabolism were rarely reported in AD, and PCA was most frequently used. The objective is to perform a data-driven analysis searching for ensembles of brain regions where a high degree of covariance in metabolic activity can be found. Once a first principal component explaining a major part of the variance in the data is obtained, subsequent orthogonal 'networks' of regions with significant covariance are looked for, and the whole variance in the images is finally explained by few components. The brain regions that significantly load on a given component can be displayed to observe a spatial distribution of each component. Each AD subject has one score for each PC. PC scores quantify the extend to which each principal component is manifested by each subject. The analyses of functional brain images in AD give surprisingly consistent results in the literature (Grady *et al.*, 1990; Sackeim *et al.*, 1993; Scarmeas *et al.*, 2004). The main components demonstrate (1) a pole restricted to posterior associative cortices (comprising the posterior cingulate cortex), (2) a pole comprising limbic structures (cingulate cortex and medial temporal regions), and (3) a pole combining posteromedial, posterolateral and frontal associative cortices. Figure 34.2 illustrates the spatial distribution of those three principal components displayed on a sagittal view of the cingulate cortex (Zuendorf, doctoral thesis, 2003). Data obtained with PCA demonstrated (1) that AD is a multivariate disease (different networks can be impaired from a metabolic viewpoint), (2) that posterior cingulate cortex is pivotal in the main components explaining the major part of the metabolic variance in AD, and (3) that activity in posterior cingulate does not always co-vary with that in medial temporal structures.

Cingulate Cortex Activity in Prodromal AD

Because memory impairment constitutes a frequent early symptom in AD, there is currently a great interest in conditions characterized by isolated decrease in memory performances. This syndrome, called amnesic MCI, questionable or possible AD, is likely to evolve (to convert) to probable AD. It is also recognized that MCI may be characterized by impairment in multiple cognitive domains or in non-memory domains, but the later patients were much less studied (Johnson *et al.*, 2004).

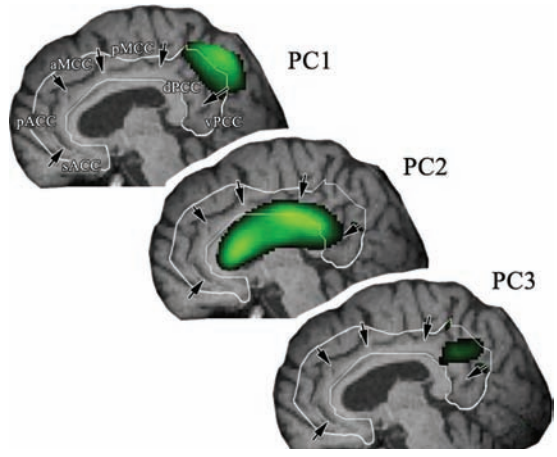

Fig. 34.2 Principal component analysis on FDG–PET images of AD patients retrospectively gathered in a single centre (Zuendorf, doctoral thesis, 2003). The first three principal components (PC) are displayed in green on a patient's sagittal MRI image and the borders of the cingulate cortex are delineated. The coloured brain regions have high load on the respective poles (significance $p<0.05$ corrected for multiple comparisons). The posterior cingulate cortex is involved in the three PCs, co-varying with different brain regions.

As highlighted in the introduction, prodromal AD can only be ascertained *a posteriori*, after longitudinal evolution of those different patients, when they have converted to AD. Initial data obtained in amnesic MCI were consistent with the early involvement of medial temporal structures in AD. MRI volume sampling with co-registered and atrophy-corrected fluorodeoxyglucose (FDG)–PET scans allowed to demonstrate that entorhinal cortex glucose metabolism and hippocampal volume were accurate variables to distinguish MCI from control population (De Santi *et al.*, 2001). Both imaging modalities identified the (lateral) temporal neocortex as best separating MCI and AD. The predictive value of FDG–PET has been further demonstrated in a longitudinal study of initially normal elderly controls (de Leon *et al.*, 2001). Subjects declining at follow-up and non-declining controls were matched for demographic variables. Glucose metabolism in the entorhinal cortex was shown to predict cognitive decline to MCI or even to AD.

Most importantly, for our discussion, hypometabolism in the posterior cingulate cortex, including the retrosplenial cortex, was also described in amnesic MCI (Minoshima *et al.*, 1997; Nestor *et al.*, 2003a,b). Accordingly, regional decrease in perfusion was most prominent among patients with 'questionable AD' who further converted to AD than in subjects with stable MCI not only in the hippocampal-amygdaloid complex, but also in the posterior cingulate, the anterior thalamus, and the ACC (Johnson *et al.*, 1998). In other studies, predominant reduction of activity was detected either in posterior cingulate and temporoparietal cortex, or in anterior cingulate and parietal cortex in MCI patients who progressed to AD (Drzezga *et al.*, 2003; Huang *et al.*, 2002; Tanaka *et al.*, 2002; Salmon *et al.*, 2007b). A discriminant analysis between questionable AD patients who did not convert, prodromal AD (with further conversion) and elderly controls showed that anterior cingulate had a greater discriminating power than posterior cingulate among the three groups (El Fakhri *et al.*, 2003). In summary, prodromal AD is characterized by decreased activity in medial temporal structures, in posterior cingulate, and also in the ACC, and we still need studies recruiting different types of 'MCI' patients to explore how heterogeneous the individual patterns of metabolic dysfunction can be, and which are their clinical correlates.

Clinical Correlates of Impaired Posterior Cingulate Metabolism in AD

Posterior cingulate hypometabolism, characteristically observed when comparing AD and control populations, was directly related to the severity of dementia in AD (Herholz *et al.*, 2002; Salmon *et al.*, 2000). Such a relationship was observed when dementia severity was evaluated with multiple-domain cognitive testing or with performances at daily living activities (Salmon *et al.*, 2005).

Were more precise clinical correlates of posterior cingulate impaired activity reported in AD patients? In the literature on functional imaging with control populations, posterior cingulate cortex was activated during working memory, episodic, autobiographic, and semantic memory tasks.

Episodic memory and cingulate activity

Impairment of episodic memory (i.e., difficulty to explicitly recall specific events in their spatial and temporal context) is a key feature of AD. Episodic memory performances in AD were related to both medial temporal and posterior cingulate glucose metabolism (Desgranges *et al.*, 1998; Lekeu *et al.*, 2003a,b). In AD patients with moderate impairment at story recall, performance was related to brain activity in parahippocampal gyrus and retrosplenial cortex (Desgranges *et al.*, 2002). A functional disconnection has been reported between frontal regions involved in strategic retrieval in episodic memory and medial temporal-based mnemonic processing (Lekeu *et al.*, 2003a); it is probable that retrosplenial involvement participates to the disconnection (Nestor *et al.*, 2003a). Figure 34.3 illustrates voxel-based linear correlation between episodic memory performance and posterior cingulate activity in a large sample of AD subjects. Although metabolism is impaired in posteromedial cortices, a modulation of posterior cingulate activity can still be observed in AD. A positive correlation has been reported between hippocampal gray matter density in AD and the increase in posterior cingulate blood flow measured during a verbal recognition memory task (Garrido *et al.*, 2002). Compared with elderly controls, Alzheimer patients showed significantly less activation in the hippocampal formation but greater activation in the medial parietal and posterior cingulate regions during the encoding of novel face–name associations (Sperling *et al.*, 2003). Repetitive learning and free recall of geometric figures was accompanied by decreased hippocampal activity, but no significant change in posterior cingulate activity in AD compared with healthy controls (Gron *et al.*, 2002). In a serial verbal recognition task performed with 75% accuracy, few AD patients showed a normal pattern of activation predominant in left anterior cingulate gyrus and anterior insula (comparable with brain activation in elderly controls), while most patients activated an alternative network comprising posterior cingulate cortex and left posterior temporal cortex (Stern *et al.*, 2000). Even in a semantic classification task, AD subjects showed a more prolonged posterior cingulate and precuneus activation than healthy subjects (Lustig *et al.*, 2003).

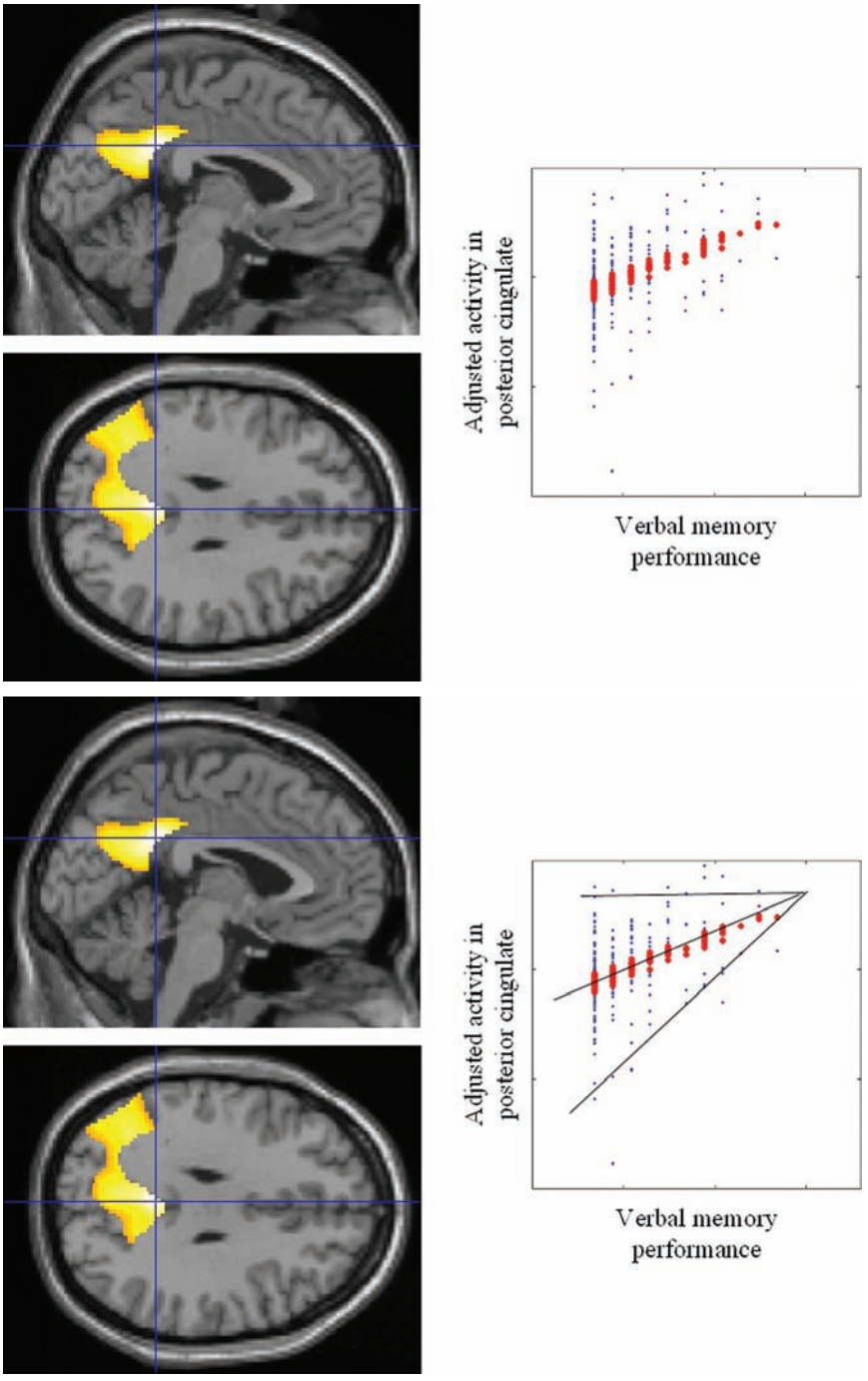

Fig. 34.3 Positive correlation between posterior cingulate activity and verbal memory performance in 209 AD patients from a European project (NEST-DD), superimposed on a sagittal and a transverse MR image. The correlation shows a continuum rather than a categorization in the relationship.

All those data were obtained with univariate analysis, assessing each region independently from the others. The Scaled Subprofile Model is a multivariate approach that allows identification of networks of regionally covarying activity across task conditions. During the performance of a serial verbal recognition task, most AD patients recruited a covariance network consisting of left posterior temporal cortex, calcarine cortex, cingulate cortex, and the vermis of the cerebellum that differed from the network activated in elderly controls (Stern *et al.*, 2000). In summary, posterior cingulate cortex can be recruited in AD for episodic memory tasks. Posterior cingulate cortex might be even more activated for some tasks in some AD patients than in control subjects, possibly to compensate dysfunction in the usual cerebral network. Functional

MRI allows one to study brain activity in single subjects; if performance is controlled, the technique might provide important information on the heterogeneity of brain function in questionable or probable AD (Lustig *et al*., 2003).

In a study of MCI patients, deficits in both encoding and retrieval were correlated with decline in hippocampal gray-matter density. The encoding subtest also correlated with hippocampal metabolism, whereas the retrieval subtest preferentially correlated with the posterior cingulate activity (Chetelat *et al*., 2003). This dissociation highlights the importance of both (interconnected) brain regions in episodic memory impairment of MCI patients.

Autobiographical memory, self, and posterior cingulate cortex in AD

Autobiographical memory is particularly impaired in AD (Piolino *et al*., 2003). More precisely, AD patients exhibit a deficit in autonoetic consciousness: they can hardly recall detailed contextual information that allows them to re-experience a personal event and makes it a unique subjective episode (Piolino *et al*., 2003; Tulving, 2002; Wheeler *et al*., 1997). Recent autobiographical memories were correlated with medial temporal activity in AD (Eustache *et al*., 2004). Additionally, a frontoparietal network comprising posterior cingulate is important for conscious awareness of information processing in human (Dehaene *et al*., 2003). Accordingly, posterior cingulate, parietal, temporal and frontal associative cortices characteristically involved in AD were suggested to subserve (conscious) controlled information processing (Salmon *et al*., 2005). In the literature on normal populations, however, posterior cingulate activity can be decreased in controlled or executive tasks when attention is directed to external stimuli rather than to 'internal' information and memories (Salmon, 2003). Accordingly, Figure 34.4 illustrates higher posterior cingulate activation in healthy controls when they read lists of meaningful words than when they had to classify words by alphabetic order (Collette *et al*., 1999).

Posterior cingulate activation might depend on self reference in cognitive tasks. This is in keeping with the selective activation of the posterior cingulate cortex during retrieval of personal semantic knowledge in control subjects (Cappa *et al*., 1998). Self reflection was also related to posterior cingulate and medial prefrontal activation in normal populations (Johnson *et al*., 2002). The self reference is in agreement with the observation that ventromedial prefrontal and posterior cingulate cortices would be activated in a 'default mode' in quiet wakefulness, when subjects are essentially engaged in self-referential thoughts (Burton *et al*., 2004). We have already mentioned that during resting state, AD patients show a decreased activity in posterior

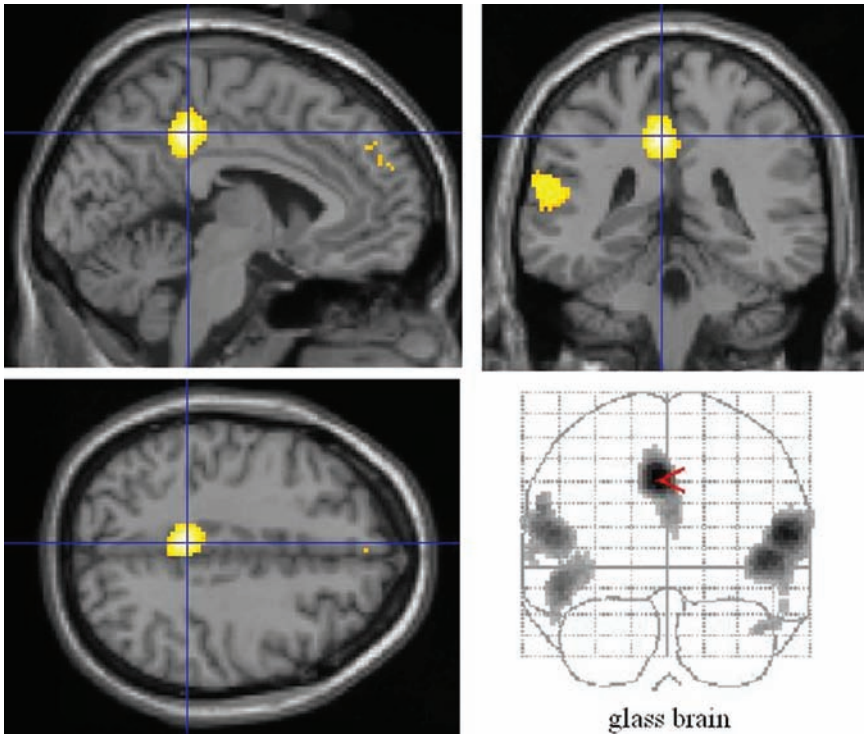

Fig. 34. 4 Posterior cingulate cortex activation was greater in healthy controls when reading word lists (probably recruiting their semantic memory) than when they alphabetically manipulated the words (i.e., when they perform an executive task driven by the visual display of the first letter). The 'glass-brain' shows that 'semantically oriented' temporal and parietal areas are also more activated when reading.

cingulate and medial temporal cortex compared with elderly controls (Greicius *et al.*, 2004). A general hypothesis derived from all those observations is that posterior cingulate involvement would participate to an impairment of self in AD, related to a decrease in autonoetic and autobiographical memory and an impairment in self reflection (Klein & Kihlstrom, 1986).

Anterior Cingulate Cortex and Behavioral Disturbances in AD

We have already pointed out that hypometabolism was less frequently reported in anterior than in posterior cingulate cortex in AD. However, a significant decrease of anterior cingulate 5HT2A receptors has been observed in AD compared with controls (Meltzer *et al.*, 1999) and decrease in anterior cingulate activity or gray matter volume was observed very early in groups of AD patients (Johnson *et al.*, 1998; Killiany *et al.*, 2000). Performance on a measure of word-reading ability, taken as an estimate of premorbid intellectual function, was inversely related to anterior cingulate metabolism in AD, when the confounding effect of dementia severity was taken into account (Alexander *et al.*, 1997). Thus, ACC (and other brain regions) might subserve a cognitive reserve influencing clinical expression of dementia.

The ACC was shown to be less involved in AD than in the subcortico-frontal dementia syndrome of Progressive Supranuclear Palsy, characterized by slowing of cognition, dysexecutive syndrome and neuropsychiatric disturbances (Salmon *et al.*, 1997). Accordingly, anterior cingulate activity was mostly involved in behavioral symptoms in AD. It was related to the degree of apathy (Benoit *et al.*, 1999, 2002; Migneco *et al.*, 2001), as illustrated in Figure 34.5, and particularly to loss of initiative (Benoit *et al.*, 2004). Depression scores obtained at the neuropsychiatric inventory (Cummings *et al.*, 1994) were also correlated to left anterior cingulate in AD (Hirono *et al.*, 1998). In another study, there was a decrease of anterior cingulate metabolism in AD patients with neuropsychiatric inventory symptoms of psychosis compared with those without psychosis (Mega *et al.*, 2000).

In summary, decreased activity in the ACC is observed in groups of patients with prodromal AD (El Fakhri *et al.*, 2003; Johnson *et al.*, 1998). We still ignore this if those patients have characteristic symptoms, but ACC involvement was essentially related to behavioral and psychiatric symptoms that can deeply impair social integration of AD patients. There is a striking contrast between memory impairment related to posterior cingulate activity in Figure 34.3 and the degree of apathy related to anterior cingulate metabolism in Figure 34.5. Behavioral and psychological symptoms, such as depression, may constitute the initial clinical abnormality in AD (Jost & Grossberg, 1996; Mega *et al.*, 1996), and we anticipate that those patients would have predominant anterior cingulate and prefrontal pathology. But cognitive and behavioral symptoms coexist in AD. The plots in Figures 34.3 and 34.5 show a gradation of symptoms and metabolic impairment more than a categorization, and subgrouping the AD population might be an oversimplification.

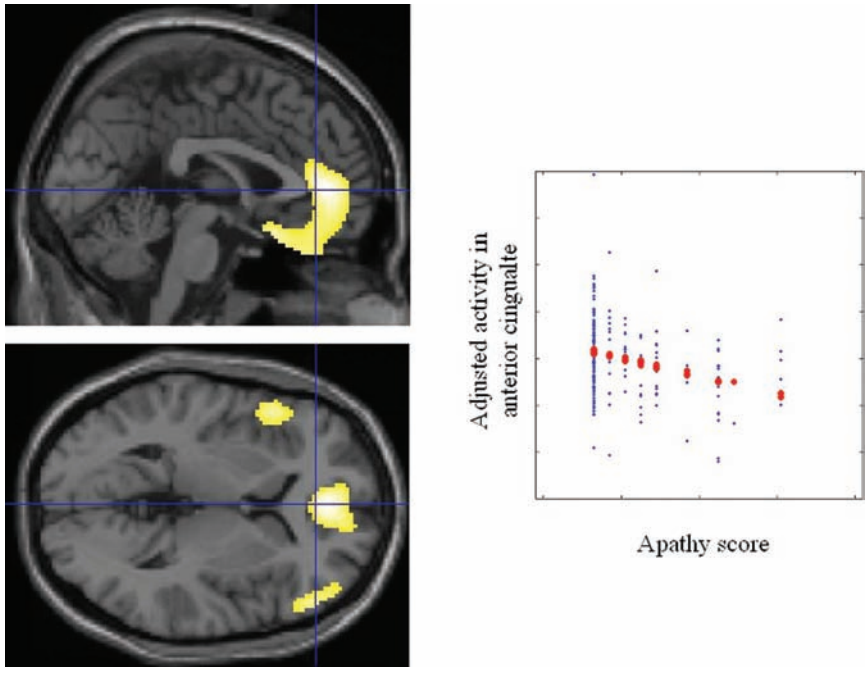

Fig. 34.5 Negative correlation between anterior cingulate metabolism and apathy score in 209 AD patients. The correlation shows a continuum rather than a categorization.

Advances in Relationships between Genotype and Cingulate Activity in AD

The epsilon-4 (E4) allele of the Apolipoprotein E (ApoE) is the most common susceptibility gene for AD. In AD, ApoE carriers have a lower metabolism than non-carriers in associative cortices such as the posterior cingulate cortex (Drzezga *et al.*, 2005). A metabolic pattern similar to that observed in AD was previously reported in cognitively normal carriers of the ApoE E4 allele who had a familial history of AD (Reiman *et al.*, 1996). Those patients were followed over an interval of approximately 2 years and they had significant decline in glucose metabolism in the vicinity of the parahippocampal gyrus, temporal, posterior cingulate and prefrontal cortices, basal forebrain, and thalamus (Reiman *et al.*, 2001). ApoE genotype has a complex influence on cingulate metabolism in MCI patients (Mosconi *et al.*, 2004). E4 carriers show a decrease in activity in posterior cingulate and temporoparietal cortices compared with non-carrier patients. But a more complex interaction exists between conversion to AD and presence of E4; 'E4 converters' have a significant reduction in anterior cingulate activity. The complex interaction shows that it may not be valid to make simple subgroups of AD patients according to a single variable. Impaired perfusion was also reported in the hippocampal complex, anterior and posterior cingulate cortices, posterior parietal lobe, and anterior frontal lobe in asymptomatic subjects with presenilin 1 mutation related to early onset AD (Johnson *et al.*, 2001).

What is now clearly missing in neuroimaging is a careful analysis of subregions of the cingulate cortex that might be related to specific clinical or genetic deficits in prodromal and probable AD.

Multiple Brain Neuroimaging Techniques for Studying AD

The posterior cingulate metabolic decrease cannot be explained by local atrophy in AD (Ibanez *et al.*, 1998). Accordingly, cerebral glucose metabolism is considered to mainly reflect loss of synaptic integrity in AD, more than local tissue loss (Salmon *et al.*, 1996). The multimodal associative posterior cingulate cortex would be particularly disconnected from medial temporal structures, for example, and also from frontal cortex (Meguro *et al.*, 1999). DTI has shown a highly significant reduction in the integrity of the association white-matter fiber tracts in the splenium of the corpus callosum, the superior longitudinal fasciculus, and the cingulum bundle in patients with probable AD relative to normal controls (Rose *et al.*, 2000). DTI might be an ideal *in vivo* technique to test the disconnection hypothesis. However, beside disconnection, there is active pathology in the posterior cingulate cortex, demonstrated in PET studies by 'inflammation like' tissue reaction (Cagnin *et al.*, 2001) and by markers of amyloid deposition in posterior cingulate (Klunk *et al.*, 2004). In late stages of the disease, regional metabolic reduction correlates with the density of neurofibrillary tangles observed postmortem (Rapoport *et al.*, 1991). Thus, the relative contribution of local pathology and functional deafferentation to decreased metabolism in posterior cingulate cortex still needs to be investigated.

New ligands for nicotinic acetylcholine receptors or for acetylcholinesterase inhibitors are available to assess different steps of the cholinergic neurotransmission, but none of the available studies described a predominance in the involvement of associative cortices, and there is yet no clear relationships established with clinical symptoms (Herholz *et al.*, 2000, 2004; Nordberg, 2003; Ota *et al.*, 2004). More specifically, no difference has been searched for between the various brain cholinergic pathways in existing studies of AD patients. Precise regional combined measurements and follow-up studies will be required to integrate data provided by the different markers.

Cingulate Cortex in the Context of Alzheimer Subgroups

Presenile and senile forms of AD have been considered as a single entity, and clinicians recognize that memory impairment is the most frequent complaint in the patients. However, most studies point also to diversity in the disease. Neuroimaging data highlighted two main pathological poles in AD, medial temporal structures, on the one hand, and associative cortices comprising the cingulate cortex, the precuneus cortex, and the lateral temporal, parietal and posterior prefrontal cortices, on the other hand. We can hardly propose a single scheme for evolution of neuroimaging abnormalities in AD, for in a recent study where selection was biased to amnesic MCI, the two pathological poles were shown to be involved simultaneously in prodromal AD, using FDG–PET images (Anchisi *et al.*, 2005). In MCI and in AD, PCA of FDG–PET revealed several principal components, corresponding to different metabolic networks impaired in the patients (Anchisi, personal communication; Zuendorf, doctoral thesis 2003; Salmon *et al.*, 2007a). Consequently, there are more than two separate pathological poles in AD. This is consistent with the fact that posterior cingulate and lateral associative cortices metabolic impairments are sometimes dissociated in AD (Salmon *et al.*, 2000).

Both the posterior and the anterior parts of the cingulate cortex are important to understand the clinical

presentation of AD; they were respectively related to cognitive and behavioral symptoms in the disease. But both cognitive and behavioral abnormalities coexist in AD. Subgrouping patients according to posterior or anterior cingulate involvement would be artificial, for clinico-metabolic correlations frequently point to gradation more than categorization in the diversity of symptoms (see Figs 34.3 and 34.5), and complex interactions exist between cingulate metabolism and disease progression (Mosconi *et al*., 2004). Then, functional imaging highlights several pathological poles in AD, which are differentially affected in each patient. Methods based on PCA, for example, could classify a FDG picture as consistent with the 'AD pattern,' but each picture would be characterized by different 'weights' for the different pathological poles. The relative weights would then be related to different clinical symptoms and different therapeutic strategies. For example, the relative involvement of ACC and the related apathetic behavior would prompt clinicians to provide an AD patient with well-organized procedures for carrying on an activity (Adam *et al*., 2000), while loss of autobiographical memory related to posterior cingulate cortex involvement would justify providing memory aids to remember activities to carry on (Quittre *et al*., 2005).

Acknowledgments

The work in the Cyclotron Research Centre was supported by grants from the European Community, the Fonds National de la Recherche Scientifique (FNRS), the University of Liege, and an InterUniversity Attraction Pole. SL is Research Associate at the FNRS.

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