Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer’s disease

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Although the patterns of structural and metabolic brain alterations in Alzheimer’s disease are being refined and discrepancies between them are being underlined, the exact relationships between atrophy and hypometabolism are still unclear. In this study, we aimed to provide a direct comparison between grey matter atrophy and hypometabolism in a sample of patients with clinically probable Alzheimer’s disease, using a voxel-based method specially designed to statistically compare the two imaging modalities. Eighteen patients with probable Alzheimer’s disease of mild severity and 15 healthy aged controls underwent both high-resolution T1 MRI and resting-state 18FDG-PET. The MRI data sets were handled using optimized VBM. The PET data were coregistered to their corresponding MRI, corrected voxel-wise for partial volume averaging and spatially normalized using the same parameters as those of their corresponding MRI volume. A differential smoothing was applied on the MRI and PET data sets to equalize their effective smoothness and resolution. For each patient, Z-score maps of atrophy and hypometabolism were created by comparing to the controls data set, respectively averaged to provide the profile of hypometabolism and atrophy, and entered in a voxel-by-voxel SPM analysis to assess the statistical differences between hypometabolism and atrophy. The observed patterns of hypometabolism and atrophy were consistent with previous studies. However, the direct comparison revealed marked regional variability in the relationship between hypometabolism and atrophy. Thus, the hypometabolism significantly exceeded atrophy in most altered structures, particularly in the posterior cingulate-precuneus, orbitofrontal, inferior temporo-parietal, parahippocampal, angular and fusiform areas. In contrast, a few hypometabolic structures among which the hippocampus exhibited similar degrees of atrophy and hypometabolism, a profile that significantly differed from the posterior cingulate. Excessive hypometabolism relative to atrophy suggests the intervention of additional hypometabolism-inducing factors, such as disconnection and amyloid deposition, resulting in genuine functional perturbation ahead of actual atrophy and perhaps of pathology as well. Conversely, in the hippocampus, where disconnection processes are also likely to occur, relative synaptic compensatory mechanisms may be taking place, maintaining neuronal activity in the face of structural alterations.

Keywords: Alzheimer’s disease; FDG-PET; MRI; hippocampus; voxel-based analysis

Abbreviations: GM = grey matter; PVE = partial volume effect; VBM = voxel-based morphometry.


Introduction

Alzheimer’s disease is associated with widespread structural and functional brain alterations. Both profiles of alterations have been well documented, with consistent regional distribution across studies. Whole-brain voxel-based MRI investigations have pointed to the medial and lateral temporal areas as the sites of highest atrophy relative to aged controls, while the parieto-temporal areas, precuneus, posterior and anterior cingulate gyri, thalamus, caudate nucleus and putamen showed significant but lower GM loss (Rombouts et al., 2000; Baron et al., 2001; Frisoni et al., 2002; Good et al., 2002; Matsuda et al., 2002; Karas et al., 2003). On the other hand, whole-brain voxel-based PET (and SPECT) investigations have pointed to the posterior cingulate-precuneus area as the highest and earliest functionally altered region. The temporo-parietal cortex is

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also significantly involved, while metabolic decreases in frontal areas develop later and remain less marked (Minoshima et al., 1997; Ibanez et al., 1998; Herholz et al., 2002; Matsuda et al., 2002; Nestor et al., 2003a; Mosconi et al., 2005; Kawachi et al., 2006). The results have been particularly discrepant regarding the hippocampal area, some studies arguing for its metabolic deterioration (Ishii et al., 1996; De Santi et al., 2001; Nestor et al., 2003a; Mosconi et al., 2005, 2006; Mevel et al., 2007) and others for its relative preservation (Minoshima et al., 1997; Ishii et al., 1998; Desgranges et al., 1998; Ibanez et al., 1998; Herholz et al., 2002; Kawachi et al., 2006).

These apparent discrepancies in the brain profiles of atrophy and hypometabolism raise two main issues. First, the divergence between the MRI and PET findings regarding the hippocampus has been highlighted as a paradox (Matsuda et al., 2002, Desgranges et al., 2004; Chételat et al., 2006; Mevel et al., 2007). Second, whether the typical posterior association metabolic defect in early Alzheimer’s disease merely reflects tissue loss is a long-held debate, which has become hotter since VBM studies have documented early atrophy also affects these areas (see debate, which has become hotter since VBM studies have documented early atrophy also affects these areas (see

**Subjects and Methods**

**Subjects**

Eighteen patients were studied, all right-handed and with at least 8 years of education. At the time of the study, none of the patients was being or had been treated with specific medication, such as anti-acetylcholinesterase agents. All were prospectively selected using standard NINCDS–ADRDA diagnostic criteria for probable Alzheimer’s disease (McKhann et al., 1984). The diagnosis of probable Alzheimer’s disease was based on an extensive neuropsychological examination which included the mini mental status examination (MMSE; Folstein et al., 1975), Mattis dementia scale (Mattis, 1976), Wechsler’s Memory scale, Story and Figure recall tests from Signoret’s battery (Signoret, 1991), verbal span (forward and backward; Signoret, 1991), verbal working memory (Brown–Peterson paradigm; Peterson and Peterson, 1959), verbal fluency (letter and category; Cardebat et al., 1990) and copy of Rey’s figure (Rey, 1959). We purposely selected patients with mild dementia, based on a MMSE score of 20 or higher. The sample consisted in 15 women and 3 men (age = 69.5±5.2, range = 60–82; MMSE = 24.3±2.6, range = 20–29). This sample partially overlaps with that of our previous articles using VBM (Baron et al., 2001), or PET (Desgranges et al., 1998) studies. Of these samples, only patients who had both PET and MRI examinations and MMSE >20 were included in the present study. Fifteen unmedicated healthy controls that also underwent both MRI and PET were also studied, all right-handed and with at least 8 years of education (eight women and seven men; age = 66.5±7.3, range = 60–84). They were screened for the absence of cerebrovascular risk factors, mental disorder, substance abuse, head trauma, significant MRI or biological abnormality and incipient dementia using a memory test battery. The two groups were matched for age and education, but women were over-represented in the Alzheimer’s disease sample compared to controls. All the subjects were fully cooperative and free from behavioural disturbances. They all gave their consent to the study after detailed information was provided to them and the PET procedure was approved by the Ethical Committee of the University of Caen. The study was done in line with the Declaration of Helsinki.

**Imaging data acquisition**

**MRI data**

For each subject, a high-resolution T1-weighted volume MRI scan was obtained, which consisted of a set of 128 adjacent axial cuts parallel to the AC–PC line and with slice thickness 1.5 mm and pixel size 1 × 1 mm (TR = 10.3 ms; TE = 2.1 ms; FOV = 24 × 18; matrix = 256 × 192). All the MRI data sets were acquired on the same scanner (1.5T Signa Advantage echospeed; General Electric). Standard correction for field inhomogeneities was applied at acquisition.

**PET data**

Each subject also underwent a PET study within days of the MRI study. Data were collected using the ECAT Exact HR+ PET device with isotropic resolution of 4.6 × 4.2 × 4.2 mm (FOV = 158 mm). The patients were fasted for at least 4 h before scanning. To minimize anxiety, the PET procedure was explained in detail beforehand. The head was positioned on a headrest according to the cantho-meatal line and gently restrained with straps. ¹⁸FDG uptake was measured in the resting condition, with eyes...
closed, in a quiet and dark environment. A catheter was introduced in a vein of the arm to inject the radiotracer. Following $^{68}$Ga transmission scans, 3–5 mCi of $^{18}$FDG were injected as a bolus at time 0, and a 10 min PET data acquisition started at 50 min post-injection period. Sixty-three planes were acquired with septa out (3D acquisition), using a voxel size of 2.2$^2$ mm$^3$ (x y z). During PET data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn over the forehead skin.

**Image handling and transformations**

The procedure detailed below has been specifically designed for the purpose of this study (see Introduction section). Its key features included (i) correction of the PET data for PVE; (ii) use of the same spatial normalization parameters for the MRI and PET data sets to avoid differences due to the normalization process or the use of different referential templates; (iii) differential smoothing of the MRI and PET data to equalize the effective smoothness of both imaging modalities data sets; and (iv) the creation of Z-score maps for each patient against the 15 controls, allowing a direct comparison of the degree of GM atrophy and hypometabolism.

To provide whole-brain profiles of atrophy and hypometabolism, both expressed in the same unit, we generated mean maps from individual Z-score maps across the sample of Alzheimer’s disease patients. Direct voxel-based comparison between the individual Z-scores of atrophy and hypometabolism was then performed using both SPM and a region-based approach. All image-processing steps were carried out by the same operators (G.C. and F.M.). A general overview of the successive steps in MRI and PET data handling and image processing is provided in Fig. 1.

**MRI data**

The MRI data sets were analysed using SPM2 and the optimized VBM protocol described in detail elsewhere (Good et al., 2001) and already used in our laboratory (Chételat et al., 2003, 2005). Briefly, the procedure included the creation of customized templates of the whole brain and the GM, WM and CSF sets using the MRI data from the whole combined patient and control samples ($n = 33$). The original MRI data sets were then segmented into SPM (implying a reversible affine normalization step) using these customized templates as priors. The resultant original (i.e. in native space) GM data sets were then spatially normalized onto the GM customized prior to determine the optimal normalization parameters, which were then applied to the corresponding original MRI scans. Finally, the ‘optimally’ normalized MRI data sets were segmented into SPM and the resultant GM partitions were masked and smoothed (see below).

**PET data**

The PET data were first corrected for PVE due to both CSF and WM using the optimal voxel-by-voxel method originally proposed by Müller-Gartner et al. (1992), and slightly modified as proposed.
by Rousset et al. (1998). This method, referred to as ‘modified Müller-Gartner’, is described in details in Quarantelli et al. (2004), and has been already applied in our laboratory (Chételat et al., 2003). All image-processing steps for PVE correction were carried out using the ‘PVE-lab’ software (Quarantelli et al., 2004).

Using SPM2, PVE-corrected PET data sets were then coregistered onto their respective MRI and spatially normalized into the same customized template as that used for the spatial normalization of MRI data, by reapplying the normalization parameters estimated from the VBM protocol. The normalized PET data sets were then masked and smoothed (14 mm; see below). Finally, the resulting PET images were divided by their individual vermis FDG uptake value to control for individual variations in global PET measures. The vermis has been selected as being the best-preserved area in Alzheimer’s disease compared to controls in preliminary analysis (data not shown), consistent with previous findings (Soininen et al., 1995; Ishii et al., 1996; Desgranges et al., 1998). The individual vermis value was obtained for each subject using the ‘Anatomical ROIs Analysis’ toolbox of SPM2 allowing the automatic extraction of the labelized region mean value from the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

**Differential smoothing**
To blur individual variations in gyral anatomy and increase the signal-to-noise ratio, the spatially normalized GM partitions and the corrected and spatially normalized PET data sets were smoothed. We used the standard Gaussian kernel of 14 mm for the PET data. Since the two data sets to be compared had different original spatial resolutions, differential smoothing was performed in order to obtain images of equivalent effective smoothness, and thus of identical resultant resolution (data not shown), consistent with previous findings (Steininen et al., 1995; Ishii et al., 1996; Desgranges et al., 1998). The individual vermis value was obtained for each subject using the ‘Anatomical ROIs Analysis’ toolbox of SPM2 allowing the automatic extraction of the labelized region mean value from the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

**Masking**
The MRI and PET images obtained following the steps above were masked so as to include only GM voxels of interest and prevent contamination by misclassified voxels as much as possible. Indeed, voxels lying at the boundary between ventricular CSF and periventricular WM tend to be misclassified as GM during the segmentation process since they tend to assume intermediate intensities (close to GM) as a result of partial voluming (see Karas et al., 2003, and Fig. 2a). The mask was obtained by thresholding the GM customized template above a value of 0.2, corresponding to a higher than 20% chance for the voxel to belong to GM. This value was selected following extensive tests as the best compromise to avoid the above misclassification because it effectively excluded the thin rim of periventricular ‘GM’ voxels (Fig. 2b), without significantly reducing the GM fraction. The same binary mask was applied to both the MRI and the PET data sets. The mask was applied twice (before and after smoothing), to avoid contamination of misclassified voxels by smoothing in the first case and big edge effects in the second case. The resultant smoothed and masked data sets were used to create the Z-score maps (see below).

**Z-score maps**
The smoothed and masked PET and MRI images were used to create Z-score maps [patient individual value – control mean)/control standard deviation], for each patient and each modality (see Kawachi et al., 2006 for a similar approach). Note that the normal distribution of control data sets used to compute Z-score maps was systematically verified in the 116 regions of the AAL labeled atlas using the ‘Anatomical ROIs Analysis’ toolbox of SPM2 (data not shown), ensuring the validity of calculating patients’ Z-scores. Individual Z-score maps were then averaged across subjects to provide the whole-brain profile of degree of GM atrophy and hypometabolism, both expressed as mean Z-scores (Fig. 3).

**Comparison between atrophy and hypometabolism Z-scores**
Statistical analyses to compare the degree of atrophy and hypometabolism using the individual Z-score maps were performed. To avoid results of non-interest in voxels with very low Z-scores, a mask image was first created from the mean Z-score
maps to include only voxels with mean MRI and/or PET $Z$-scores $\leq -1.5$, and then applied to the individual $Z$-score maps.

The masked atrophy and hypometabolism individual $Z$-score maps were then entered in an SPM paired $t$-test analysis (‘multi-subjects: conditions and covariates’ routine), with one group (Alzheimer’s disease) and two images per subject, i.e. the PET and MRI $Z$-score maps. Note that sex is implicitly modelled as confound in this sort of statistical design. Both contrasts were assessed ($Z$-PET $< Z$-MRI and $Z$-MRI $< Z$PET), and statistical

maps were thresholded using a $P < 0.05$ (voxel-level) FDR corrected for multiple comparisons threshold (Fig. 4).

So as to provide quantitative insight into the regional atrophy and hypometabolism $Z$-scores over and above the voxel-based analysis, the regional mean $Z$-scores for PET and MRI were extracted from the masked images (i.e. in regions of mean MRI and/or PET $Z$-scores $<-1.5$), using automatic regional labelling (Anatomical Automatic Labeling; Tzourio-Mazoyer et al., 2002) and extraction (anatomical ROI analysis toolbox in SPM2) procedures, after normalization of the anatomically labelled MNI template onto our customized template (Fig. 5 and Table 1). Paired $t$-tests were conducted for each region to compare the MRI and the PET mean $Z$-scores (Table 1).

Finally, in order to specifically assess whether there was a significant difference between the relative degree of atrophy and hypometabolism in the hippocampus compared to the posterior cingulate cortex (see Introduction section), we conducted a repeated-measures ANOVA with two factors (Region and Modality) of two levels each (Hippocampus versus Posterior Cingulate, and Z-MRI versus Z-TEP) from the extracted mean $Z$-scores for these two structures (Fig. 6).

Fig. 3 Mean MRI (atrophy; top) and PET (hypometabolism; bottom) $Z$-score maps, as projected onto surface rendering and axial views of the customized MRI template. Note that the 3D surface renderings falsely suggest the presence of atrophy and hypometabolism in the corpus callosum, which is in fact related to volume averaging in this anatomically variable area. Right is right.

Fig. 4 Glass-brain representation of the results of the SPM comparison between individual MRI and PET $Z$-score maps showing significant differences for the hypometabolism $>$ atrophy contrast (top) and projection of the corresponding SPM-T map onto axial views of the customized MRI template (bottom). The $T$-value of 2.34 used as threshold in the Figure corresponds to the $P$ (FDR-corrected) $< 0.05$ threshold described in the text. Right is right.
Anatomical localization was based on the superimposition of the mean atrophy, mean hypometabolism and SPM-T maps onto the customized template using the publicly available ‘Anatomist/BrainVISA’ software (www.brainvisa.info), and identification of the localization using anatomical atlases.

**Results**

**Atrophy**

The mean atrophy Z-score map is illustrated in Fig. 3, and the mean regional atrophy Z-scores are listed in Table 1. Areas of highest GM loss (Z-scores $\leq -2$ in some portions) were found in the hippocampus (specifically in its superior-lateral part), amygdala, posterior part of the caudal anterior cingulate, thalamus, parts of the middle frontal gyrus, putamen, and superior temporal and orbito-frontal cortices. Intermediate Z-scores ($-1$ to $-2$) were found in parts of the insula, caudate nucleus, supramarginal gyrus, rostral anterior and posterior cingulate, precuneus, middle and inferior temporal, lingual, fusiform, parahippocampal and superior and inferior frontal gyri. The remaining parts of the brain, with Z-scores $>-1$, mainly involved the primary cortical areas (occipital and pre- and post-central regions), the cuneus and cerebellum, also encroaching the lingual, fusiform, angular and superior and inferior parietal gyri. The mean regional Z-scores listed in Table 1 are consistent with this pattern.

**Hypometabolism**

The mean hypometabolism Z-score map is illustrated in Fig. 3 and the mean regional hypometabolism Z-scores are listed in Table 1. The posterior cingulate-precuneus area, extending to the caudal anterior cingulate cortex, showed the highest metabolic decrease (Z-scores $<-2$). Marked declines also concerned the caudate nucleus, middle temporal gyrus (also involving the superior temporal gyrus, in the left hemisphere), posterior parahippocampal cortex and hippocampus, gyrus rectus and right insula. Z-scores between $-1$ and $-2$ were found in the left insula and remaining temporal cortices, amygdala, thalamus, supramarginal gyrus, angular gyrus, frontal areas (mainly orbitofrontal and middle frontal gyri), rostral anterior cingulate, lingual and fusiform gyri. Smaller changes (Z-scores $>-1$) were observed in most remaining GM areas, including the putamen, pallidum and most of the occipital cortex, with lowest ratios being obtained in the pre- and post-central gyri and cerebellum. The mean regional Z-scores were consistent with this pattern (Table 1).

**Comparison between atrophy and hypometabolism Z-scores**

The direct SPM comparison between MRI and PET Z-scores (only including voxels with mean Z-MRI and/or Z-PET $<-1.5$), illustrated in Fig. 4, revealed significant differences for the hypometabolism>atrophy contrast only. The brain areas most involved were the posterior cingulate and precuneus, the inferior parietal and angular gyri (predominantly right-sided), the medial orbito-frontal areas (i.e. gyrus rectus, medial orbito-frontal, superior medial frontal and olfactory gyri and the anterior cingulate cortex), and the fusiform and middle and inferior temporal gyri (predominantly right-sided). Less significant differences were also found in the parahippocampal and lingual gyri, temporal pole, middle and superior medial frontal areas and caudate nucleus.
As illustrated in Fig. 5 (see also Table 1), the extracted mean regional Z-scores were entirely consistent, with the vast majority of altered regions demonstrating significantly lower PET than MRI Z-scores, with only slight differences with the voxel-based results due to regional sampling. The hippocampus was among the few structures not showing higher hypometabolism than atrophy.

The results of the ANOVA conducted on extracted posterior cingulate and hippocampus MRI and PET Z-scores showed a significant interaction between the two factors (Region × Modality), indicating that the relative degree of atrophy and hypometabolism significantly differed between these two structures, with lower PET than MRI Z-scores for the posterior cingulate only (Fig. 6).

**Discussion**

Previous MRI and PET studies in Alzheimer’s disease have led to quite consistent findings regarding the pattern of brain atrophy on the one hand, and that of hypometabolism on the other (see Introduction). Similarities of both effects in some brain regions, but striking discrepancies in others, have also been highlighted. Our aim here was to provide an objective and quantitative assessment of these relationships in Alzheimer’s disease. To this end, we have designed a novel procedure using Z-score maps and their direct statistical comparison. Over and above a broad overlap in the respective patterns of atrophy and hypometabolism, our findings point to striking and highly significant regional differences in their relative degree. Specifically, most altered brain regions, such as the posterior cingulate gyrus-precuneus and orbito-medial frontal areas, expressed greater hypometabolism than atrophy, in contrast with other regions such as the hippocampus, which exhibited no significant difference. Thus, the relationship between these changes is not uniform across the brain, suggesting that superimposed hypometabolism-inducing factors such as disconnection operate in the
former regions, while functional compensatory processes probably develop in the latter.

**Methodological issues**

In this study, we specifically designed a procedure to directly compare the relative amounts of hypometabolism and atrophy throughout the brain. We implemented optimal image data handling for both MRI and PET, including optimized VBM for the former (Good et al., 2001) and voxel-based PVE correction taking into account both spill-in and spill-out effects for the latter (Quarantelli et al., 2004). To prevent artefacts as far as possible due to misclassification of voxels in GM nuclei, particularly in periventricular areas, the masking procedure was applied both before and after smoothing. Only minor differences in atrophy Z-scores were observed if the mask was applied only after smoothing as classically performed (data not shown), the ‘double-masking’ procedure leading to a very slight increase in atrophy Z-scores. Methodological improvements specific to the hypometabolism versus atrophy comparison purpose were also implemented. Thus, spatially normalizing both imaging data sets using the same optimal parameters prevents artefacts due to differences in the accuracy of the normalization process or in the reference templates. Additionally, the difference in resolution between both modalities was taken into account by applying differential smoothing on the two data sets. Finally, generating Z-score maps accounted for the fact that the two data sets do not have the same normative values, and thus allowed a direct statistical and quantitative comparison between the degrees of atrophy and hypometabolism.

Despite these methodological measures, we cannot exclude the possibility that voxel misclassification in deep grey nuclei may partially account for their apparent marked atrophy (and trend for higher atrophy than hypometabolism) in the present study. Even though significant atrophy of the caudate (Rombouts et al., 2000, Baron et al., 2001; Karas et al., 2003), thalamus (Baron et al., 2001; Karas et al., 2003), putamen (Baron et al., 2001) and pallidum (Teipel et al., 2005) has been reported in previous MRI studies, these nuclei are particularly prone to artefacts due to their boundary position between white matter and ventricles, potentially leading to misclassification of voxels as false negatives, or deformations due to ventricular size enlargement (Frisoni et al., 2002; Good et al., 2002; Karas et al., 2003). Thus, our findings for these structures will not be further discussed.

Our patient and control samples did not have comparable sex ratios. Although not directly addressed here, this difference should not have significantly influenced our findings given that the effect of sex on brain metabolic alterations in Alzheimer’s disease is negligible compared to disease effects (see Minoshima et al., 1997, for instance).

**Similarities between the atrophy and hypometabolism profiles**

Over and above striking differences to be discussed below, there was overall an extensive overlap between these two profiles. Thus, structural and metabolic alterations essentially involved the hippocampal region, cingulate gyrus, basal ganglia, temporal neocortex, insula and middle and orbital frontal areas, while the cerebellum, primary sensorimotor, premotor and occipital cortical areas were best preserved in both modalities. This broad similarity of altered and preserved cerebral regions suggests that common mechanisms participate in both processes, and/or that a causal relationship exists between atrophy and hypometabolism. Although the intimate relationship between cortical atrophy and glucose hypometabolism in neurodegenerative disorders is not known, intuitively a relationship is expected since in these conditions the former mainly reflects loss of neurons and/or synapses (Bobinski et al., 1996, 2000) and the latter reflects decrease in synaptic density/activity (Rocher et al., 2003). The broad similarity between the patterns of atrophy and hypometabolism observed in the present study is therefore consistent with this general idea. Furthermore, more complex relationships between atrophy and hypometabolism could be envisaged. For instance, the biochemical mechanism(s) that lead up to
progressive neuronal loss may also induce local hypometabolism, and conversely any prolonged metabolic disruption may in turn lead to neuronal loss (see Chételat et al., 2005 for further discussion). However, it has also been shown that glucose hypometabolism can result from disconnection, suggesting potentially superimposed effects of disconnection onto direct effects of neuronal/synaptic loss (see below).

**Differences between profiles**

If hypometabolism and atrophy were evenly related without added region-specific interference from modulating factors, one would expect a linear relationship between both processes throughout the brain, i.e. no regional variation in the difference between the degrees of atrophy and hypometabolism. Instead, we found considerable and highly significant regional variabilities, suggesting that additional processes interact to alter the hypometabolism–atrophy relationship in a regionally specific way.

**Sites of greater hypometabolism compared to atrophy**

The vast majority of regions altered either structurally or metabolically (i.e. with mean Z-scores < −1.5) showed significantly greater hypometabolism than atrophy, and this effect was particularly marked in the posterior cingulate-precuneus, gyrus rectus, medial and orbito-frontal, inferior parietal and angular gyri, inferior temporal cortex and parahippocampal and fusiform gyri. That hypometabolism was more severe than atrophy in these areas as compared to the rest of the brain suggests some functional alteration (be it metabolic, chemical or molecular) takes place specifically in these regions over and above neuronal/synaptic loss, enhancing in some way the metabolic counterpart of local atrophy. Although one could argue that since there is no background knowledge of the ‘physiologically expected’ relationship between the degree of atrophy and that of hypometabolism, this discrepancy could reflect instead a lack of functional compensation relative to the remaining brain areas, there are strong arguments in the literature that favour our hypothesis. Several studies indicate that distant effects of atrophy (or pathology) on glucose metabolism through functional disruption of connected areas contribute to the hypometabolic pattern observed in Alzheimer’s disease (Minoshima et al., 1997; Meguro et al., 1999; Matsuda, 2001; Smith, 2002; Chételat et al., 2003, 2006; Nestor et al., 2003b). Specifically, the well-described posterior association hypometabolism could in part reflect remote effects from the connected but atrophied hippocampus. Several lines of evidence support this hypothesis (Meguro et al., 1999, 2001; Garrido et al., 2002; Rémy et al., 2005; Hirao et al., 2006), which the regional specificity found here further reinforces. Explicitly, the regions showing the most significant predominance of hypometabolism are those highly connected to the hippocampus through the cingulum bundle (Kobayashi et al., 2003, 2007; Schmahlmann et al., 2007).

Over and above disconnection, there is only limited available molecular or histopathological data to make any additional robust hypothesis regarding the mechanisms underlying this disproportionate hypometabolism. A few studies have reported deficits in muscarinic receptors (Claus et al., 1997; Boundy et al., 2005) and glutamate neurotransmission (Hattori et al., 2002; Lin et al., 2003) in these brain regions in Alzheimer’s disease. However, recent 11C-PIB PET studies of amyloid load have reported a pattern of alteration that includes regions of higher hypometabolism revealed here, i.e. the posterior cingulate and orbito-frontal regions (Buckner et al., 2005; Price et al., 2005; Mintun et al., 2006; Ziolko et al., 2006). Moreover, the level of amyloid deposition was found to inversely correlate with glucose metabolism in some brain areas such as the parietal cortex (Klunk et al., 2004; Engler et al., 2006). Although this relationship was not found for all brain regions (e.g. for the frontal cortex), it suggests that amyloid deposition may contribute to the functional disruption conducting to disproportionate hypometabolism, either directly or by preventing functional compensation mechanisms (see below).

**Insight on the hippocampus**

We found the hippocampus to exhibit significant atrophy and hypometabolism of similar magnitude for both modalities. The structural alteration of the medial temporal grey structures was entirely expected based on numerous prior reports (Rombouts et al., 2000; Baron et al., 2001, Frisoni et al., 2002; Good et al., 2002; Chételat and Baron, 2003; Karas et al., 2003) and is widely thought to reflect early neurofibrillary pathology (Bobinski M et al., 1996; Braak and Braak, 1996). In contrast, the metabolic alteration of this region is less well established since a number of previous PET studies failed to evidence significant relative hippocampal hypometabolism (see Introduction section). However, using a rigorous methodology including PVE correction, optimal normalization and the vermis as reference, has permitted the subtle hypometabolism present in this complex and small structure, particularly sensitive to methodological issues, to be consistently detected in several recent studies (Ishii et al., 1998; De Santi et al., 2001; Nestor et al., 2003a; Mosconi et al., 2005; Mevel et al., 2007). Nonetheless, even though genuine hypometabolism was detected in the hippocampus using stringent methodology, this region was far from being the most severely affected of all brain regions in spite of it being the most structurally impaired, pointing to a discrepancy opposite to that characterizing the posterior cingulate.

Thus, in sharp contrast with the vast majority of regions, the hippocampus was among the very few not showing
higher metabolic than structural alteration with either the SPM or the ROI-based analysis (Fig. 4, Table 1). This finding could either indicate a lack of additional functional perturbation (such as disconnection phenomenon) in this structure (compared to brain areas of highest discrepancy), or the additional occurrence of functional compensation mechanisms, which is more strongly supported by the following lines of evidence. The entorhinal cortex, which provides its main input to the hippocampus (particularly the gyrus dentatus and CA subfields; Duvernoy, 1988), is known in Alzheimer’s disease to be affected by atrophy at least as early and severely as the hippocampus (see Chetelat and Baron, 2003, for review). Thus, the same disconnection phenomenon as that speculated to enhance relative hypometabolism for the posterior cingulate would be expected to affect also the hippocampus. Quite conversely, however, there was a highly significant interaction between both disease manifestations. However, that hypometabolism exceeds atrophy in most areas suggests the intervention of additional hypometabolism-inducing factors, leading to genuine functional disruption in early Alzheimer’s disease ahead of actual atrophy, and perhaps of pathology as well. Synaptic suppression secondary to medial temporal damage, and possibly other local alterations including amyloid deposition, may take place in areas such as the posterior cingulate-precuneus and medial orbito-frontal regions resulting in greater hypometabolism than atrophy. Conversely, the hippocampus did not show this dissociation, suggesting that compensatory mechanisms may unfold there to maintain function of the remaining synapses despite evolving disconnection.

**Conclusion**

Altogether, our findings highlight overlapping profiles of metabolic and structural alterations, suggesting overlapping pathological mechanisms and/or causal relationship between both disease manifestations. However, that hypometabolism exceeds atrophy in most areas suggests the intervention of additional hypometabolism-inducing factors, leading to genuine functional disruption in early Alzheimer’s disease ahead of actual atrophy, and perhaps of pathology as well. Synaptic suppression secondary to medial temporal damage, and possibly other local alterations including amyloid deposition, may take place in areas such as the posterior cingulate-precuneus and medial orbito-frontal regions resulting in greater hypometabolism than atrophy. Conversely, the hippocampus did not show this dissociation, suggesting that compensatory mechanisms may unfold there to maintain function of the remaining synapses despite evolving disconnection.

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