A Voxel-based Morphometric Study to Determine Individual Differences in Gray Matter Density Associated with Age and Cognitive Change Over Time

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Voxel-based morphometry (VBM) was used to examine the relation between age and gray matter density cross-sectionally and to study the association between gray matter density and longitudinal decline in performance on cognitive tests in healthy, non-demented elderly individuals. Participants were neuropsychologically tested at baseline and again after 3 years. Thirty-seven subjects (mean age 72.5 years) who showed a decline in cognitive test performance at follow-up were compared with 38 individually matched control subjects (mean age 71.8 years) whose performance did not change over time. Magnetic resonance imaging scans were acquired at follow-up and individual differences in regional gray matter density were examined with VBM. The largest age effects were found in various regions in the prefrontal cortex, the (medial) temporal lobes and the striate cortex. Longitudinal cognitive decline was associated with decreased gray matter density in prefrontal areas, the (medial) temporal lobes and the posterior parietal cortex. These findings suggest that prefrontal and temporal cortical regions are of particular relevance both in aging and age-related cognitive decline in healthy elderly individuals.

Keywords: aging, cognitive decline, gray matter, voxel-based morphometry

Introduction

A large number of *in vivo* imaging studies [using computed tomography (CT) or magnetic resonance imaging (MRI)] have considered age-related changes in the whole brain (e.g. Jernigan *et al.*, 1991, 2001; Coffey *et al.*, 1992, 1998; Courchesne *et al.*, 2000; Resnick *et al.*, 2000; Tisserand *et al.*, 2000a) as well as gray and white matter separately (e.g. Jernigan *et al.*, 1991, 2001; Raz *et al.*, 1997; Guttmann *et al.*, 1998; Courchesne *et al.*, 2000; Resnick *et al.*, 2000; Good *et al.*, 2001). Furthermore, effects of age on specific regions of interest have been reported, such as the hippocampus (Raz *et al.*, 1997; Jack *et al.*, 1998; Tisserand *et al.*, 2000b; Ylikoski *et al.*, 2000; Pruessner *et al.*, 2001), prefrontal lobes (Raz *et al.*, 1997; Salat *et al.*, 1999, 2001; Tisserand *et al.*, 2001, 2002), striatum (Gunning-Dixon *et al.*, 1998) and thalamus (Van der Werf *et al.*, 2001). It has been suggested that volume decreases in the prefrontal cortex (PFC) are a characteristic of the normal aging process, whereas atrophy of medial temporal lobe (MTL) regions is specifically related to pathological aging (Raz, 2000). However, the extent to which regional decreases in brain volume occur in normal aging and whether the rate of decline differs per region are still a matter of debate.

The majority of imaging studies on aging have used volumetric approaches to determine individual regional differences. The strength of volumetry is that the regions of interest can be precisely outlined, even if there is large intersubject anatomical variation. A disadvantage is the labor intensiveness of such approaches, which makes them unattractive for the analysis of large datasets (e.g. Tisserand *et al.*, 2002). Also, as a consequence, generally only a limited number of regions is measured in each of these volumetric studies. Finally, regions with ill-defined anatomical boundaries, such as the insular cortex, have been largely ignored. These problems can possibly be overcome by using whole-brain analysis methods such as voxel-based morphometry (VBM). VBM is a relatively recently developed technique to examine regional differences in tissue density throughout the brain (Wright *et al.*, 1995; Ashburner and Friston, 2000). It has been used to characterize morphometric differences between individuals on a voxel-by-voxel basis, for instance due to normal aging (Resnick *et al.*, 2000; Good *et al.*, 2001; Goto *et al.*, 2001; Tisserand *et al.*, 2002) and due to pathological conditions, such as Alzheimer's disease (e.g. Rombouts *et al.*, 2000; Thompson *et al.*, 2001). These studies have proven successful in localizing anatomical differences between (groups of) individuals.

Most imaging studies have been cross-sectional by nature and therefore one can only speculate about the relation between brain atrophy and age-related cognitive decline. Moreover, it is still not clear whether a direct relation exists between age-related volume losses and cognitive change over time. Some studies have found an association between regional brain volumes and cognitive functioning, for instance hippocampal volume and memory performance (Golomb *et al.*, 1994) and volume of the prefrontal lobes and mental imagery (Raz *et al.*, 1999). However, most studies have not found evidence for such a relation between brain volume and cognitive performance after adjusting for age effects (Raz *et al.*, 1998; Petersen *et al.*, 2000; Tisserand *et al.*, 2000b; Ylikoski *et al.*, 2000). The purpose of the present study was to evaluate the relation between age-related regional cortical differences and cognitive change over time. VBM was used (i) to consider the association between age and gray matter density cross-sectionally in healthy, non-demented individuals and (ii) to study the relation between gray matter density and longitudinal decline in performance on cognitive tests. It was hypothesized that the largest age effects on gray matter density would be found within the PFC, while cognitive decline would be particularly associated with decreased gray matter density in the MTL.

Materials and Methods

Subjects

Participants were drawn from a larger study on determinants of cognitive aging, the Maastricht Aging Study (MAAS). The aims, population sample and design of this study have been described in detail elsewhere (Jolles *et al.*, 1995; Van Boxtel *et al.*, 1998). In short, 1877 participants were drawn from a register of family practices in the

south of The Netherlands (Metsemakers *et al.*, 1992). All individuals were aged between 24 and 81 years at baseline and were, according to the practitioner's information, without medical conditions that could interfere with normal cognitive function. People were excluded in the case of (a history of) chronic neurological pathology (e.g. dementia, cerebrovascular disease, epilepsy, parkinsonism and malignancies related to the nervous system), mental retardation or chronic psychotropic drug use. In addition, a score on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) <24 also resulted in exclusion. The sample was stratified according to age (5 year age groups), sex and general ability level. All participants underwent medical and neuropsychological assessment. Of this group, 838 individuals aged 49 years or older at baseline were re-examined after 3 years. For the present study, at this point a selection was made of participants who showed an individual decline on tests of objective cognitive function, using the baseline assessment 3 years earlier as a reference. The criteria for decline were defined as follows: (i) a score of 24 or lower or a decline of at least three points on the MMSE and/or (ii) a decline of at least 30% on two or more of six core tests that were used in MAAS to probe different cognitive domains: verbal memory (immediate and delayed recall; Brand and Jolles, 1985); verbal fluency (animal naming; Luteijn and Van der Ploeg, 1983); basic processing speed (letter digit substitution test; Smith, 1968) and complex information processing (concept shifting digits/letters; Houx *et al.*, 1991); and Stroop interference (Stroop, 1935) (for a full description of these tests, see Jolles *et al.*, 1995). Forty-four individuals who were thus identified as cognitive 'decliners' were matched for age, sex and educational level as closely as possible to other participants from the MAAS study who showed no decline according to these criteria. None of the participants in this study fulfilled the DSM-IV criteria for dementia (American Psychiatric Association, 1994). All 88 individuals were invited to the Maastricht University Hospital for an additional MRI session within 4 weeks of the cognitive screening. All MRI scans were inspected by a neuroradiologist for clinically relevant abnormalities. Seven individuals in the case group and six in the control group were excluded from further analysis because of movement artifacts (n = 8) and anatomical abnormalities (n = 5). Thus, 37 cases and 38 controls proceeded to the VBM analysis.

Written informed consent was obtained from all participants, for the MAAS study and this additional scan study separately. The MAAS protocol and the additional scan protocol were approved by the Medical Ethics Committee of the Maastricht University Hospital.

MRI Acquisition and Analysis

MRI scans were acquired with a 1.5 T Gyroscan NT MRI scanner (Philips, Best, The Netherlands). T_1-weighted images were obtained in the coronal plane [perpendicular to the anterior commissure–posterior commissure (AC–PC) line]. A 3D-gradient fast field echo (FFE) sequence was applied with T_R = 35 ms, T_E = 7 ms and a flip angle of 35°. Slice thickness was 1.5 mm with no interslice gap. The image matrix was 256 × 256 and the field of view 240 mm. Hence, voxel size was 0.94 × 0.94 × 1.5 mm.

To prepare the original images for the VBM analysis, a number of preprocessing steps were applied. First, the image volumes were corrected for MR signal non-uniformities due to magnetic field inhomogeneities in the scanner (Sled *et al.*, 1998). Secondly, the original images were linearly transformed into stereotaxic space (Talairach and Tournoux, 1988) using an automatic registration program developed at the McConnell Brain Imaging Center of the Montreal Neurological Institute (Collins *et al.*, 1994). This transformation results in an alignment along the AC–PC axis and accounts for individual differences in global brain size and shape. This resampling resulted in MRI volumes consisting of 181 axial slices, with an isotropic voxel size of 1 mm^3. Thirdly, images were classified into gray matter, white matter and cerebrospinal fluid (CSF) partitions, by means of an automatic tissue classifier algorithm (Evans *et al.*, 1996; Collins and Evans, 1999). This procedure included the removal of all extracranial tissue and the cerebellum and has been validated previously (Collins *et al.*, 1994). Finally, a binary map of all gray matter voxels was extracted from each classified image and this gray matter map was smoothed using a Gaussian kernel of 10 mm full-width at half-maximum. Smoothing converts the binary data into a range of continuous data, which is required for the statistical procedures in VBM, which are based upon Gaussian random field theory. Furthermore, smoothing also reduces the effect of individual variation in the exact location of gyri and sulci (Watkins *et al.*, 2001). These smoothed gray matter density maps were used to localize age-related volume losses. VBM analyses were performed with software developed at the Montreal Neurological Institute, as previously described (Paus *et al.*, 1999; Pruessner *et al.*, 2001; Watkins *et al.*, 2001; Golestani *et al.*, 2002; Tisserand *et al.*, 2002).

Statistical Analysis

Baseline characteristics of the two groups (Table 1) were compared with groupwise t-tests for continuous variables (age and educational level) and a χ^2 test (sex). MMSE scores at baseline in both groups were compared with a non-parametric test (Mann–Whitney). A general linear model was fitted for all six cognitive variables combined measured at baseline, to test an overall effect of 'caseness' on cognitive functioning. Analyses were performed using a P-level of 0.05.

The effect of age on total volume of the gray matter, white matter and CSF was examined in the healthy, 'non-decliner' group, with linear regression models (Table 2). Differences in these volumes between the two groups were assessed with groupwise t-tests. To examine whether the spatial transformation had an influence on the findings, analyses were repeated with the native image volumes. This was done by transforming the normalized images back into native space using the formula: native_image = normalized_image/($sx \times sy \times sz$), where sx, sy and sz are the scaling factors of the linear transformation (Pruessner *et al.*, 2001).

To localize the age-related changes in gray matter density in the non-decliner group with the VBM approach, a linear regression model was applied to the normalized and smoothed gray matter maps of these subjects (Wright *et al.*, 1995; Paus *et al.*, 1999; Ashburner and Friston, 2000). This method, based upon Gaussian random field theory, corrects for multiple comparisons in a given search volume, in this case the gray matter maps of all subjects (Friston *et al.*, 1996; Worsley *et al.*, 1996). The statistical significance of the relation between age and gray matter density was assessed for each voxel,

Table 1
Demographical characteristics (mean ± SD) at follow-up of the study sample

	Decliners (n = 37)	Non-decliners (n = 38)
Age (years)	72.5 ± 7.9	71.8 ± 7.7
Age range (years)	53–84	52–82
Sex (M/F ratio)	19/18	18/20
Educational level[a]	2.4 ± 1.4	2.5 ± 1.7

[a]Educational level range: 1–8 (elementary education/scientific education). Scores between 2 and 3 are equivalent to lower vocational education/intermediate secondary education (De Bie, 1987).

Table 2
Global tissue characteristics (volumes in cm^3, mean ± SD) of the study sample (n = 75) and variance explained by age (R^2) after adjusting for the influence of sex in the non-decliner group

Brain volume	Decliners (n = 37)	Non-decliners (n = 38)	R^2 age
Gray matter	541.07 ± 150.7	603.73 ± 103.4*	0.21**
White matter	712.92 ± 127.9	703.2 ± 64.0	0.01
Cerebrospinal fluid	195.17 ± 70.2	160.82 ± 40.8*	0.31**
Scaling factor[a]	1.10 ± 0.4	1.10 ± 0.7	0.00

[a]The scaling factor represents the linear transformation vector which was computed to spatially normalize the images.
*P < 0.05; **P < 0.001.

after removal of the effect of sex. Differences between the decliner and non-decliner groups were examined in a similar fashion, while adjusting for the effects of sex and age.

Because our hypotheses were specifically directed at the PFC and MTL, we focused on these predefined regions of interest. Based upon our previous work a search region of 25 cm^3 was used, which roughly corresponds to the combined volume of the hippocampus and PFC in young adults, transformed into Talairach space (Pruessner *et al.*, 2000, 2001; Tisserand *et al.*, 2000b, 2002). As a result, to reach a significance level of $P < 0.05$ corrected for multiple comparisons, *t*-values were thresholded at 3.73 (Worsley *et al.*, 1996).

Results

The two groups did not differ with respect to age, sex or educational level (Table 1). MMSE score at baseline was not different between 'decliners' and 'non-decliners' (Mann–Whitney $U = 648.0$, n.s.) and neither was the general linear model fitted for caseness to test group differences on all six cognitive tests scores at baseline combined [Hotelling's $T = 0.134$, $F(6,66) = 1.471$, n.s]. Hence, at baseline, the groups did not significantly differ with respect to the performance on any of the cognitive measures. By definition, significant group differences were found at follow-up. In the group of decliners, 20 individuals were included based on the MMSE-criterion only, 14 based on the cognitive test criterion only and three individuals met both criteria.

An age effect on global tissue volumes (Table 2) was found for the gray matter ($R^2 = 0.21$, $P < 0.001$) and CSF ($R^2 = 0.31$, $P < 0.001$), but not for the white matter ($R^2 = 0.01$, n.s.). Likewise, global differences between the 'decliners' and 'non-decliners' were found in the gray matter (541 versus 604 cm^3, respectively, $P < 0.05$) and CSF (195 versus 161 cm^3, $P < 0.05$), but not in the white matter (713 versus 703 cm^3, n.s.). Performing the analyses with the native instead of normalized data did not change the results (data not shown). This was not surprising, given the fact that the scaling factor (used for the spatial transformation) was not different between the groups and was not significantly related to age.

Increasing age was associated with decreases in gray matter density throughout the brain, but the magnitude of the effect greatly differed across regions. The largest age-related decreases in the non-decliner group ($P < 0.0001$; Table 3 and Fig. 1) in gray matter density were found in various frontal regions (right frontal pole, left dorsolateral PFC, anterior cingulate and the anterior part of the insula bilaterally), in the temporal lobes (left hippocampus and middle and superior temporal gyrus) and in the striate cortex. Differences in gray matter density between the cognitive decliners and non-decliners were most prominent ($P < 0.05$; Table 4 and Fig. 2) in the PFC (left frontal pole, right inferior frontal gyrus, and right dorsolateral PFC), in the right temporal lobe (hippocampus and posterior temporal) and in the right posterior parietal cortex. The difference between the groups for the left hippocampus approached significance ($t = 3.5$, $P = 0.10$).

Table 3
Negative associations ($t < -4.75$; $P < 0.001$) between gray matter density and age ($n = 38$)

Cortical region	BA	*x*	*y*	*z*	*t*-value
Frontal pole	L10	–25	62	–10	–5.18
	R10	24	63	5	–5.76
	M10/11	–3	61	–13	–5.05
Insula	L	–45	25	–2	–5.44
	R	41	26	–1	–5.31
Anterior cingulate	M24/32	–2	23	39	–5.27
Dorsolateral PFC	R9/44	51	18	25	–5.13
	L6	–53	5	26	–5.80
Middle temporal gyrus	L21	–56	–12	–6	–6.70
Hippocampus	L	–23	–20	–16	–5.99
	R	21	–22	–15	–5.05
Superior temporal gyrus	R22	67	–38	18	–5.36
Medial occipital lobe	M19	–10	–74	28	–6.07

Note: *x*, *y*, *z* are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t*-value). BA, approximate Brodmann areas; L, left; R, right; M, midline.

Discussion

In a group of healthy individuals >50 years of age, a global decrease in gray but not white matter was found. The greatest decreases in gray matter density were located in the PFC and the (medial) temporal lobes, as well as in the striate cortex. Age-related volume decreases in the region of the MTL have been reported in a number of studies (Jernigan *et al.*, 1991, 2001; Raz *et al.*, 1997; Jack *et al.*, 1998; Tisserand *et al.*, 2000b; Ylikoski *et al.*, 2000; Pruessner *et al.*, 2001), especially in samples including older adults (e.g. Mueller *et al.*, 1998; Mu *et al.*, 1999; Jernigan *et al.*, 2001). Smaller lateral temporal volumes in older individuals have also been noted before (e.g. Raz *et al.*, 1997; Jernigan *et al.*, 2001). The gray matter density decrease in specific parts of the PFC is in line with previous volumetric studies which have found a disproportionate effect of age on this region (Raz *et al.*, 1997; Tisserand *et al.*, 2001, 2002). VBM has been used in several other studies to study age effects (Resnick *et al.*, 2000; Good *et al.*, 2001; Goto *et al.*, 2001; Tisserand *et al.*, 2002). For instance, in a sample including 465 subjects (Good *et al.*, 2001), the greatest decreases in gray matter density were found in the frontal and temporal cortex, which supports the results of the present study. However, contrary to our findings, these authors reported a relative preservation of the MTL region. An explanation for this discrepancy is the fact that the study by Good *et al.* (2001) involved subjects aged 20–80 years, while in the present study they were all 50 years and over. As mentioned before, age-related volume losses in the MTL region seem to accelerate in older adults (Mueller *et al.*, 1998; Mu *et al.*, 1999; Jernigan *et al.*, 2001) and therefore may appear to be only mild or even go unnoticed in studies with subjects across the complete adult age range.

Cognitive change over time was associated with global reductions in gray but not white matter volume. The areas of greatest difference in gray matter density between cognitive 'decliners' and 'non-decliners' were located in the PFC, the (medial) temporal lobe and posterior parietal cortex. Several studies have considered differences between healthy elderly and subjects with mild cognitive impairments in regional brain volumes. A significant reduction in the volume of the hippocampus (Parnetti *et al.*, 1996) and parahippocampal gyrus (Visser *et al.*, 1999) was observed in subjects with mild cognitive impairments compared with healthy age-matched

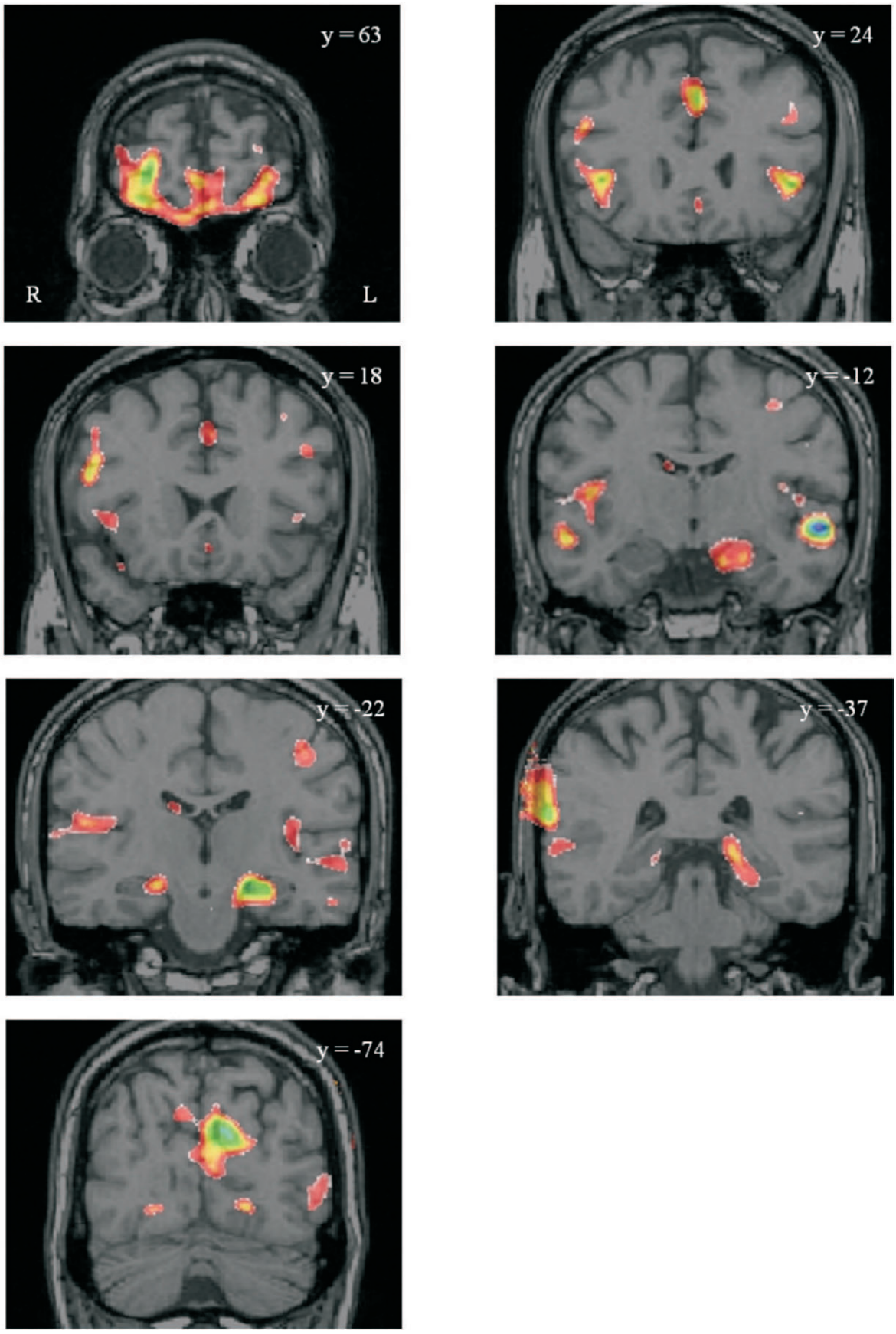

Figure 1. Regions where a significant relation was found between increasing age and a decrease in gray matter density ($n = 38$). Orange and red: $-4.0 > t > -4.5$; green and yellow: $-4.5 > t > -6.0$; purple and blue: $t < -6.0$.

Table 4
Areas where gray matter density was lower in 'decliners' than in 'non-decliners' ($t > 3.73$; $P < 0.05$; $n = 75$)

Cortical region	BA	*x*	*y*	*z*	*t*-value
Frontal pole	L10	–36	52	2	3.99
	L10	–21	53	–10	4.27
Inferior frontal	R45	59	26	16	4.29
	R44	62	8	15	4.05
Dorsolateral PFC	R6	33	–1	46	4.48
Hippocampus	R	25	–16	–19	3.99
Inferior temporal gyrus	R37	64	–45	–12	3.90
Posterior parietal cortex	R19/39	34	–70	31	4.14

Note: *x*, *y*, *z* are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t*-value). BA, approximate Brodmann areas; L, left; R, right.

controls. However, other studies did not find evidence for such volume differences between cognitively healthy and mildly impaired individuals in the medial temporal lobes (Soininen *et al.*, 1994), nor in the frontal cortex (Hänninen *et al.*, 1997).

To our knowledge, this is the first study to examine the relation between longitudinal decline in cognitive functioning and differences in gray matter density throughout the brain. In the only imaging study with a design similar to ours (i.e. a longitudinal selection of participants), it was found that a reduction in the volume of the hippocampus was not significantly related to cognitive decline in healthy elderly individuals (Ylikoski *et al.*, 2000). In that study, no other brain regions were measured. The fact that the strongest effects both of age and cognitive decline were found in the prefrontal cortex and (medial) temporal lobes confirmed our hypothesis that these regions are of particular relevance in aging and age-related cognitive decline. However, we expected that the PFC would be especially implicated in aging and the MTL in cognitive decline, but this prediction was not supported by the data. Advancing age and cognitive decline had a similar effect on gray matter density in MTL and PFC regions. It may be hypothesized that volume decreases in the PFC characterize normal aging processes during adult life (Raz, 2000) and that MTL atrophy only becomes apparent in older individuals. The combined effect of these regional volume losses may subsequently lead to functional decline.

Methodological Issues

The obvious advantage of VBM is that it is fast and automated and therefore applicable to large samples, including hundreds of subjects (e.g. Good *et al.*, 2001; Goto *et al.*, 2001). Also, there is no need for a priori hypotheses about regions of interest because differences are assessed throughout the cortex. Furthermore, VBM is a very sensitive approach to detect differences in irregularly shaped brain regions. For instance, in the present study as well as in the study by Good *et al.* (2001), a strong negative relation between age and the insula was observed. This region has anatomical boundaries that are difficult to define and trace and, consequently, it has largely been ignored in volumetric studies. Finally, VBM can localize interindividual differences within regions (as demonstrated with respect to aging by Pruessner *et al.*, 2001; Tisserand *et al.*, 2002). For instance, in our previous study which focused on the frontal lobes (Tisserand *et al.*, 2002) the strongest age-related decreases in gray matter density were found in the frontal pole (R > L) and anterior cingulate region, a pattern that is supported by the present findings. However, a limitation of the method is that, in contrast to what its name suggests, VBM does not offer the possibility of quantifying brain volumes. In addition, large anatomical variability in the location even of primary sulci and gyri (Ono *et al.*, 1990; Rajkowska and Goldman-Rakic, 1995; Roland *et al.*, 1997) hampers the interpretation of VBM studies. Consequently, coregistration accuracy is a point of continuing concern and discussion (e.g. Ashburner and Friston, 2001; Bookstein, 2001).

To illustrate this, a probabilistic map was created on the basis of the gray matter maps of the non-decliner group (Fig. 3). This map displays the probability for each voxel of being classified as gray matter. Regions with high probabilities ($P > 0.7$) were observed along the longitudinal fissure, in the temporal lobes (especially the MTL) and in the ventral parts of the frontal and parietal cortices. Low probabilities ($P < 0.4$) were found in the dorsal part of the frontal and parietal lobes and in the occipital lobes. The fact that the probabilistic map shows low values particularly in the dorsal part of the brain can be explained by two factors: (i) sulcal variability in the middle and superior frontal gyri is larger than in other parts of the cortex, or (ii) tissue classification has not been completely successful due to signal non-uniformity in the dorsal–ventral direction. The first factor points to 'anatomical noise', while the second factor can be designated 'artifactual noise'. To examine whether the results could be explained on the basis of artifactual noise, the gray matter maps were compared with the original, non-classified images to determine whether striking misclassifications could be observed. Such errors, which should have occurred repeatedly to explain the findings of the probabilistic map, were not apparent. Moreover, during the preprocessing, images were corrected for signal nonuniformity using a well-validated method (Sled *et al.*, 1998). Therefore, it seems unlikely that the low values in the probabilistic map are due to classification errors. Evidence in favor of a anatomical explanation for lower probability values in the dorsal part of the cortex comes from a study by Thompson *et al.* (2001), in which normal variability in cortical patterns was examined using 3D displacement maps. Variability was found to be highly region-dependent, with only slight variance in the primary motor and sensory areas and orbitofrontal cortex and the largest variability in the superior and middle frontal gyri and posterior parietal region. Hence, the present findings are in line with those of Thompson *et al.* (2001).

In sum, anatomical variability leads to regionally fluctuating statistical power to detect individual differences with age or between groups with VBM. As a consequence, in areas with large anatomical variability (such as the superior frontal lobes), differences in gray matter density may have been overlooked (type I error). Nonetheless, in the regions that do show differences the effect must be robust and, therefore, it seems safe to conclude that aging and age-related cognitive decline differentially affect prefrontal and temporal cortical regions.

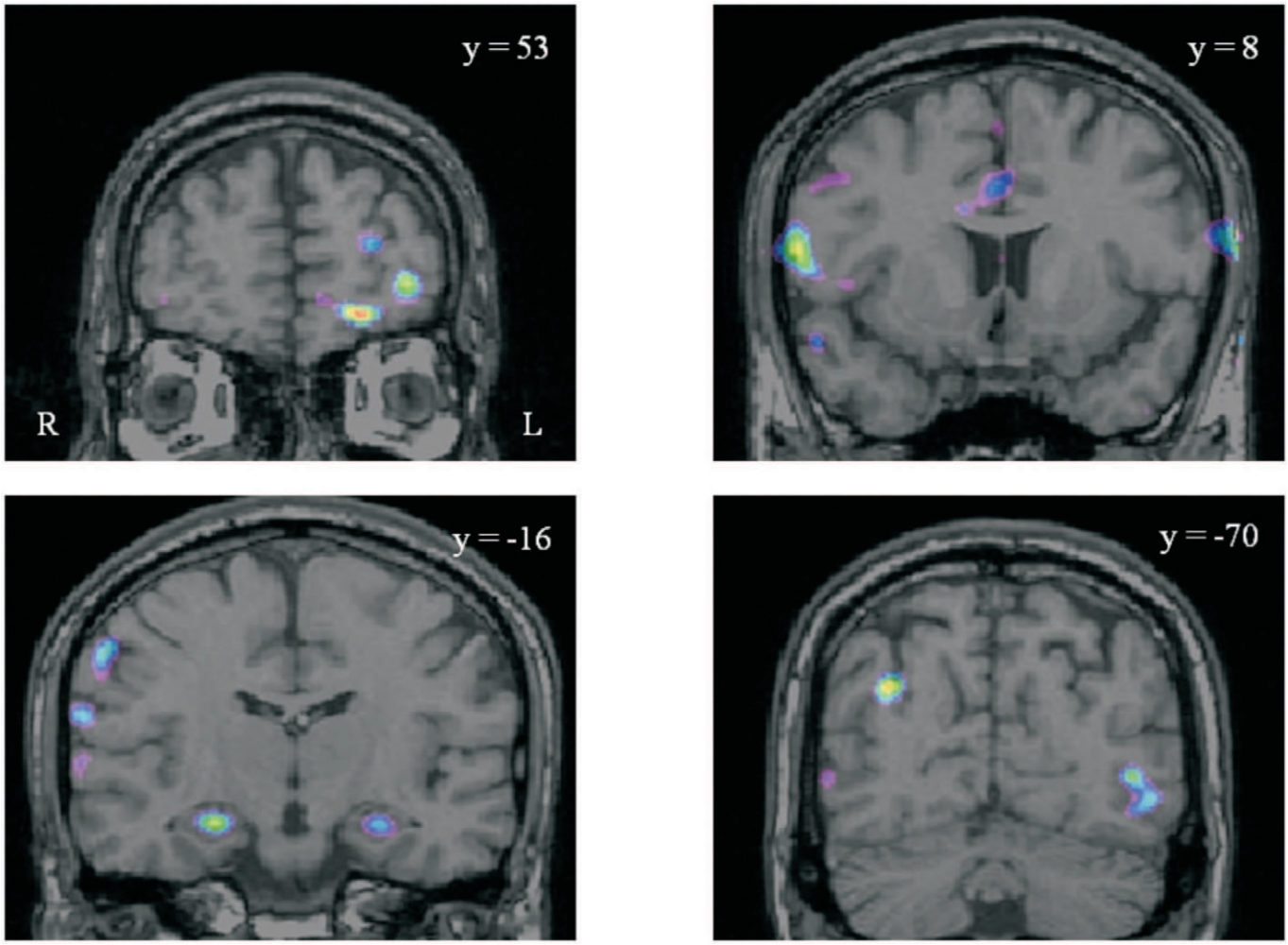

Figure 2. Regions where a significant reduction was found in gray matter density in the decliner versus non-decliner groups ($n = 75$). Purple and blue: $-3.0 > t > -3.5$; green and yellow: $-3.5 > t > -4.1$; orange and red: $t < -4.1$.

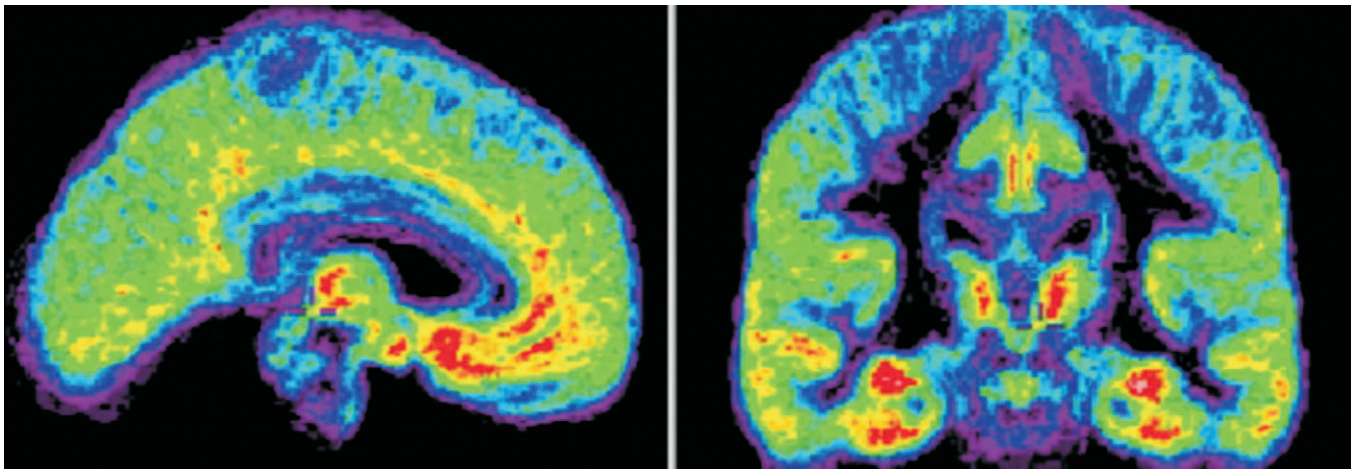

Figure 3. Probabilistic map on the basis of the gray matter maps of the healthy group ($n = 38$). Colors represent the probability of a certain voxel to be classified as gray matter. Purple and blue: $P < 0.5$; green and yellow: $0.5 < P < 0.8$; orange and red: $P > 0.8$.

Notes

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