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

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 grey matter density were examined with VBM. The largest age effects were found in various regions in the prefrontal cortex, (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, where 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 (Metsmakers 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 from further analysis because of movement artifacts. Seven individuals in the case group and six in the control group were inspected by a neuroradiologist for clinically relevant abnormalities. 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/((1-sz)*E + 1). 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/((1-sz)*E + 1).

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 z^2 test (sex). MMSE scores at baseline in both groups were equivalent to lower vocational education/intermediate secondary education (De Bie, 1987). The statistical significance of the relation between age and gray matter density was assessed for each voxel, 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).

### Table 1

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decliners (n = 37)</th>
<th>Non-decliners (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.5 ± 7.9</td>
<td>71.8 ± 7.7</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>53–84</td>
<td>52–82</td>
</tr>
<tr>
<td>Sex (M/F ratio)</td>
<td>19/18</td>
<td>18/20</td>
</tr>
<tr>
<td>Educational level*</td>
<td>2.4 ± 1.4</td>
<td>2.5 ± 1.7</td>
</tr>
</tbody>
</table>

*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 cm³; mean ± SD) of the study sample (n = 75) and variance explained by age (R²) after adjusting for the influence of sex in the non-decliner group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decliners (n = 37)</th>
<th>Non-decliners (n = 38)</th>
<th>R² age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>541.07 ± 150.7</td>
<td>603.73 ± 103.4*</td>
<td>0.21**</td>
</tr>
<tr>
<td>White matter</td>
<td>712.92 ± 127.9</td>
<td>703.2 ± 64.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>195.17 ± 70.2</td>
<td>160.82 ± 40.8*</td>
<td>0.31**</td>
</tr>
<tr>
<td>Scoring factor</td>
<td>1.10 ± 0.4</td>
<td>1.10 ± 0.7</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The scaling factor represents the linear transformation vector which was computed to spatially normalize the images. 

*P < 0.05; **P < 0.001.

**MRI Acquisition and Analysis**

MRI scans were acquired with a 1.5 T Gyroscan NT MRI scanner (Philips, Best, The Netherlands). A 3D-gradient fast field echo (FFE) sequence was applied with \( T_1 = 55 \text{ ms}, T_2 = 7 \text{ ms} \) 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 mm³. 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
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 cm³ 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; 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 $5.73$ (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 declinvers, 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 spatial transformation did not differ between the groups.

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 ($t = 3.5$, $P = 0.10$).

### 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; Yliskoski 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

### Table 3

<table>
<thead>
<tr>
<th>Cortical region</th>
<th>BA</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$t$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal pole</td>
<td>L10</td>
<td>−25</td>
<td>62</td>
<td>−10</td>
<td>−5.18</td>
</tr>
<tr>
<td>R10</td>
<td>24</td>
<td>63</td>
<td>5</td>
<td>5.76</td>
<td></td>
</tr>
<tr>
<td>M10/11</td>
<td>−3</td>
<td>61</td>
<td>−13</td>
<td>5.05</td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>L</td>
<td>−45</td>
<td>25</td>
<td>−2</td>
<td>−5.44</td>
</tr>
<tr>
<td>R</td>
<td>41</td>
<td>26</td>
<td>−1</td>
<td>−5.31</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>M24/32</td>
<td>−2</td>
<td>23</td>
<td>39</td>
<td>−5.27</td>
</tr>
<tr>
<td>Dorsolateral PFC</td>
<td>R9/44</td>
<td>51</td>
<td>18</td>
<td>25</td>
<td>−5.13</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>L6</td>
<td>−53</td>
<td>5</td>
<td>26</td>
<td>−5.80</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>L</td>
<td>−23</td>
<td>−20</td>
<td>−16</td>
<td>−5.99</td>
</tr>
<tr>
<td>R</td>
<td>21</td>
<td>−22</td>
<td>−15</td>
<td>−5.05</td>
<td></td>
</tr>
<tr>
<td>Medial occipital lobe</td>
<td>R22</td>
<td>67</td>
<td>−38</td>
<td>18</td>
<td>−5.36</td>
</tr>
</tbody>
</table>

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.
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: $t < -6.0$. 
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 the prefrontal 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 non-uniformity 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.

### 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

### Table 4

<table>
<thead>
<tr>
<th>Cortical region</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal pole</td>
<td>L10</td>
<td>−36</td>
<td>52</td>
<td>2</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td>R10</td>
<td>−21</td>
<td>53</td>
<td>−10</td>
<td>4.27</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>R45</td>
<td>59</td>
<td>26</td>
<td>16</td>
<td>4.29</td>
</tr>
<tr>
<td></td>
<td>R44</td>
<td>62</td>
<td>8</td>
<td>15</td>
<td>4.05</td>
</tr>
<tr>
<td>Dorsolateral PFC</td>
<td>R6</td>
<td>33</td>
<td>−1</td>
<td>46</td>
<td>4.48</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>R</td>
<td>25</td>
<td>−16</td>
<td>−19</td>
<td>3.99</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>R37</td>
<td>64</td>
<td>−45</td>
<td>−12</td>
<td>3.90</td>
</tr>
<tr>
<td>Posterior parietal cortex</td>
<td>R19/39</td>
<td>34</td>
<td>−70</td>
<td>31</td>
<td>4.14</td>
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</tbody>
</table>

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.
**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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References


De Bie SE (1987) Standaardvragen 1987: Voorstellen voor unifor-

mering van vraagstellingen naar achtergrondkenmerken en inter-


Folstein MF, Folstein SE, McHugh PR (1975) ‘Mini-mental state’: a practical method for grading the cognitive state of patients for the clini-


Lutjens F, Van der Ploeg FAE (1983) Handling Gift (Groninger Intel-


MRS, MRI-based hippocampal volumetry, and 99mTc-HMPAO-


Raz N (2000) Ageing of the brain and its impact on cognitive perform-


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