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Prefrontal cortex atrophy predicts dementia over a six-year period

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Abstract

The present study investigated prefrontal cortex (PFC) atrophy as a possible predictor of dementia. Eighty-eight older participants of the Maastricht Aging Study (MAAS) were administered for neuropsychological tests at baseline and after three years (t_3). Magnetic resonance images were acquired at t_3 and nine years after baseline all participants were screened for dementia. Three groups were distinguished: (1) participants who did not develop dementia or cognitive decline, (2) participants who did not develop dementia but did show significant cognitive decline, and (3) participants who developed dementia. Gray matter volume of structures in the PFC and medial temporal lobe (MTL) was measured. Prefrontal volume was significantly smaller in group 3 than in the other two groups, and PFC volume was significantly better than MTL volume in distinguishing between groups 2 and 3. These findings suggest that PFC atrophy is highly associated with dementia and can be considered an important predictor of the disease. It may even be a better predictor than the MTL atrophy that has been found in earlier studies.
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1. Introduction

A large number of structural brain imaging studies on cognitive aging and dementia have focused on the degeneration of the medial temporal lobe (MTL) (DeCarli et al., 2007; Korf et al., 2004; Visser et al., 2002). Far less attention has been paid to neurodegenerative changes in the various structures present in the prefrontal cortex (PFC). While PFC atrophy is frequently reported in studies on healthy aging (Raz et al., 2005; Tisserand et al., 2002), much less is known about neurodegenerative changes in the PFC and its predictive value for pathological aging. It has been suggested that degeneration of the structures in the PFC may characterise the normal aging process, whereas atrophy of the MTL may be specifically related to dementia (Raz, 2000).

The purpose of the present nine-year longitudinal study was to investigate PFC atrophy as a predictor of dementia. Here, the term 'predictor' is intended as a biomarker of dementia, which does not imply a causal relationship between PFC atrophy and dementia. We compared three groups of older individuals, namely: (1) participants who did not develop dementia or cognitive decline, (2) participants who did not develop dementia but did demonstrate significant cognitive decline, and (3) participants who developed dementia. The gray matter volume was measured in several contiguous substructures in the PFC (inferior prefrontal cortex, orbital prefrontal cortex, dorsolateral prefrontal cortex and anterior cingulate gyrus) and MTL (hippocampus and parahippocampal gyrus) that are known to be highly asso-

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ciated with age-related decline. For this purpose, we used a novel semi-automatic tracing method.

2. Methods

2.1. Participants

Eighty-eight healthy and non-demented subjects were selected from a large longitudinal study on determinants of cognitive aging, the Maastricht Aging Study (MAAS). The aims, population characteristics and design of MAAS have been described in detail elsewhere (Jolles et al., 1995; Van Boxtel et al., 1998). In short, MAAS encompasses approximately 1900 healthy subjects aged 25–80. The subjects are tested four times by a neuropsychological assessment (at baseline, three-year follow-up, six-year follow-up and twelve-year follow-up) and evaluated by a questionnaire at the nine-year follow-up. MAAS is currently conducting its twelve-year follow-up. The data included in the study reported here were derived from the baseline assessment (t_0), the three-year follow-up (t_3) and the nine-year follow-up (t_9). Data collection was performed in two phases. In the first phase, forty-four individuals who were identified as cognitive 'decliners', were matched for age, sex and educational level to forty-four control subjects. Differences in performance on two extensive neuropsychological assessments performed three years apart (t_0 and t_3) were used

to determine the criteria for decline. Cognitive decline was therefore defined as follows: (1) a score of 24 or lower at follow-up or a decline of at least three points on the mini-mental state examination (MMSE); or (2) a decline of at least 30% on two or more of six core tests used in MAAS to probe the following cognitive domains: verbal memory (verbal learning test, immediate and delayed recall), verbal fluency (animal naming), basic processing speed (letter digit substitution test), and complex information processing (concept shifting test and stroop interference test) (Jolles et al., 1995).

In the second phase, all eighty-eight individuals initially selected were invited to come to the Maastricht University Hospital for an MRI scan within four weeks after the second cognitive screening (t_3). Seven decliners and six control subjects were excluded from further analysis because of MRI movement artefacts ($n = 8$) or neuroanatomical abnormalities ($n = 5$). Nine years after the baseline assessment (t_9, i.e. six years after the scan-session) the remaining 75 participants were checked for dementia. Ten participants (seven decliners and three control subjects) were diagnosed with dementia (APA, 1994). The aetiology of the diagnoses was judged by an experienced neuropsychiatrist from Maastricht University Hospital (FRJV). This neuropsychiatrist diagnosed according to the standard criteria, and based the diagnosis on the available neuropsychological data as well as data on daily functioning and the participant's medical profile (i.e. medical history, comorbidity, course, and MRI scan). The

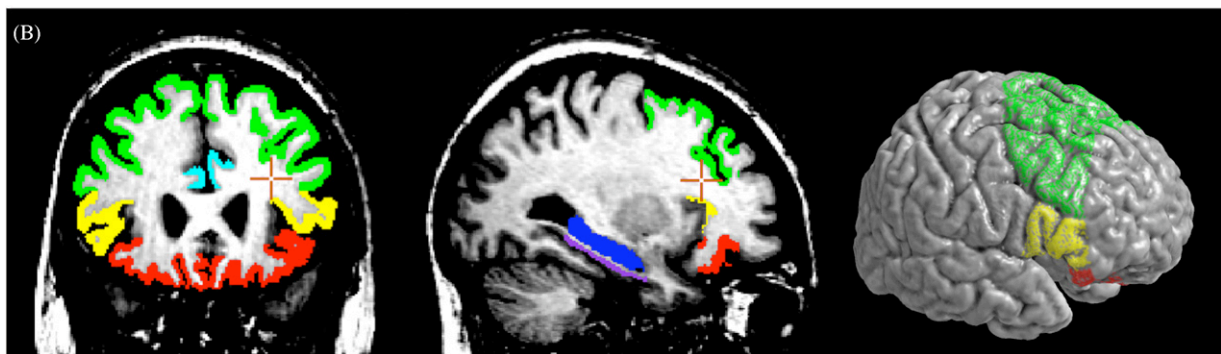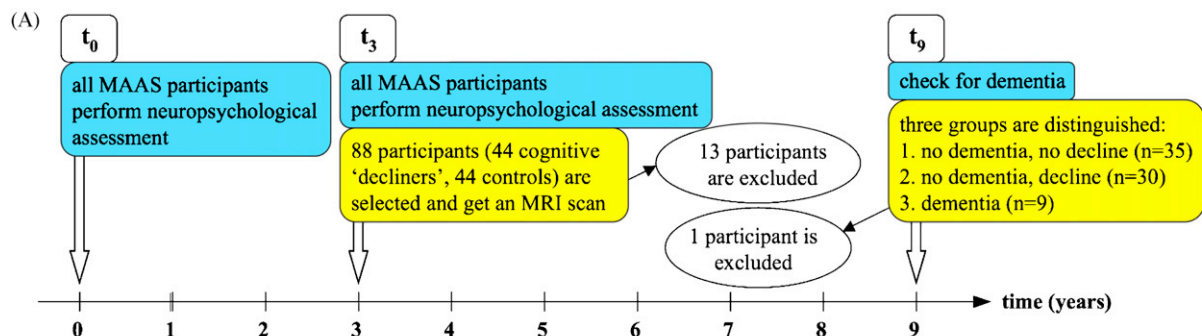Fig. 1. Summary of the methods. The top panel (A) shows the study's time path and assignment of participants to the study groups. The bottom panel (B) shows the regions of interest that were traced, namely: inferior prefrontal cortex (yellow), orbital prefrontal cortex (red), dorsolateral prefrontal cortex (green), hippocampus (dark blue), parahippocampal gyrus (purple) and anterior cingulate gyrus (light blue).

profile of nine participants was compatible with probable Alzheimer's disease (AD) or possible AD/mixed type dementia (McKhann et al., 1984). The profile of one participant matched possible frontotemporal dementia. This subject was excluded so that we could attribute our findings to AD. The group of nine participants that had developed dementia was considered post hoc to be a separate category, thereby yielding three groups for the analyses: (1) participants who did not develop dementia or cognitive decline ($n = 35$, 19 females); (2) participants who did not develop dementia but did demonstrate significant cognitive decline ($n = 30$, 14 females); and (3) participants who developed dementia ($n = 9$, 4 females). The selection of participants and the study's time path are summarised in Fig. 1A. With respect to the cognitive decline group (group 2), 18 individuals were included based on the MMSE-criterion only, 11 based on the cognitive test criterion only, and 1 individual met both criteria. Written informed consent was obtained from all participants. Both the MAAS-protocol and the additional scan protocol were approved by the local Medical Ethics Committee.

2.2. MRI acquisition and analysis

MRI scans were acquired at t_3 with a 1.5 T Gyroscan NT MRI scanner (Philips, Best, the Netherlands). T1-weighted images were obtained in the coronal plane (perpendicular to the anterior commissure-posterior commissure [AC-PC] line) using a 3D-gradient fast field echo (FFE) sequence (TR = 35 ms, TE = 7 ms, FA = 35, FOV = 240 mm, slice thickness = 1.5 mm, matrix size = 256×256, voxel size = 0.94 mm $\times$ 0.94 mm $\times$ 1.5 mm). The image volumes were corrected for MR signal nonuniformities caused by magnetic field inhomogeneities in the scanner (Sled et al., 1998). As our tracing method was semi-automatic, it was required to keep the contrast and brightness of the displayed images constant. Therefore, standardizing of grayscale intensities was performed (Nyúl and Udupa, 1999).

Six brain areas (Fig. 1B) were traced by using the following criteria:

Inferior PFC (∼Brodmann areas 44 and 45): The posterior border was defined by the precentral sulcus and the anterior border by the frontal pole region. The frontal pole region has no clear macroscopical anatomical landmarks. Therefore, a straight line was drawn to mark the posterior border of the frontal pole. This straight line was drawn upwards from the anterior top of the cingulate sulcus. The inferior frontal sulcus was taken as the dorsal border, the horizontal ramus of the Sylvian fissure as the ventral border (Uylings et al., 2005). *Orbital PFC (∼Brodmann areas 47, 11 and 12)*: Based upon cytoarchitectonic experience (HBMU), the posterior border was defined by a straight line that was drawn downwards from the inner curvature of the corpus callosum. The anterior border consisted of the frontal pole region. Medially, this region was bounded by the ventral part of the anterior cingulate region. The lateral border was anteriorly the horizontal ramus of the Sylvian fissure and posteriorly the circular

sulcus of the insula (Tisserand et al., 2002). *'Dorsolateral PFC' (∼Brodmann areas 8, 9, 46 and part of 6)*: This region has as the lateral ventral border, the inferior frontal sulcus, and as medial border, the (interrupted) paracingulate sulcus. The posterior border was defined by the precentral sulcus, and the anterior border by the frontal pole region (Tisserand et al., 2002). *Anterior cingulate gyrus (∼Brodmann area 24 and 33)*: Cingulate gyrus borders were set between the ventral and dorsal banks of the callosal sulcus and the cingulate sulcus. The most caudal coronal slice on which the posterior commisure was visible was used to subdivide the anterior cingulate gyrus from the posterior cingulate gyrus (Jones et al., 2006). *Hippocampus*: The volume of the hippocampus included the hippocampus proper (including the dentate gyrus), the alveus, and the subiculum. The anterior and posterior borders were based on both sagittal and coronal sections of the brain (Insausti et al., 1998; Visser et al., 1999). *Parahippocampal gyrus*: Tracing of the parahippocampal gyrus was performed on every coronal slice on which the hippocampus was visible. The subiculum was taken as the dorsal border and the collateral sulcus as the ventral border (Insausti et al., 1998; Visser et al., 1999).

The three-dimensional boundaries (contours) of the regions of interest were drawn manually using the DISPLAY software package (Montreal Neurological Institutep; http://www.bic.mni.mcgill.ca/software/). The defined contours were used to trace gray matter with a tool of the custom software package GIANT, developed at the Maastricht School for Mental Health and Neuroscience (Gronenschild et al., in preparation). This tool labels all voxels inside a manually drawn contour that are classified as gray matter. This classification is performed by the INSECT package developed at Montreal Neurological Institute (Zijdenbos et al., 2002). The results were then displayed by GIANT as overlays on the original stack in a triplanar view. All results were verified slice-by-slice and corrected manually if necessary. Ten randomly selected brains were measured twice and these yielded high test-retest reliability (intraclass correlation coefficients, ICC (Shrout and Fleiss, 1979), for all brain areas > 0.95).

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc, Chicago), version 15.0 for Windows. Firstly, the baseline characteristics were calculated with independent *t*-tests (continuous variables) and Chi-square tests (categorical variables). Secondly, volumetric comparisons among the three groups were performed using general linear models (GLM). The group differences for each individual brain area were calculated with Univariate GLM, with 'volume of a certain brain area' (corrected for intracranial volume) as dependent variable, 'group' as independent variable and 'age' as covariate. Thirdly, a comparison of group differences between the total MTL volume and the total PFC volume was calculated with Repeated Measures GLM. In this analysis, 'volume' was the dependent variable with PFC volume and MTL volume as the two measurements, and 'group' was the independent variable. The interaction-

effect of 'volume' and 'group' indicated whether there was a significant larger group difference in the PFC than in the MTL or the other way around. All tests were performed two-sided with an alpha of 0.05 and met the assumptions of parametric tests.

3. Results

3.1. Group characteristics

Table 1 shows the characteristics of the three groups studied at a three years time interval (at baseline, t_0, and after three years, t_3). The three groups did not differ significantly with respect to sex, educational level and intracranial volume. The mean age of participants who developed dementia was significantly higher than that of participants who did not develop dementia (73.8 and 69.1 years at baseline, $t = 2.704$, $p = 0.015$). We therefore adjusted the analyses for age by including age as a covariate. Since men in this study had significantly larger intracranial volumes than women (1128 versus 1003 cm^3, $t = 4.834$, $p \leq 0.001$), all volumes were expressed as the percentage of the intracranial volume. These percentages were used in all analyses.

With respect to the six cognitive tests, group 1 (no dementia, no cognitive decline) did not differ from group 2 (no dementia, significant cognitive decline) at baseline, except for one memory subtask: group 1 performed significantly better than group 2 on the verbal learning test – delayed

recall (9.26 versus 7.93, $t = -2.01$, $p = 0.05$). However, group 3 (dementia at t_9) did differ significantly from the other two groups with respect to several cognitive tests. When compared to group 1, group 3 performed significantly poorer at baseline on all cognitive tests ($p < 0.05$), except for verbal fluency (18.0 versus 21.9, $t = -1.869$, $p = 0.069$). Group 3 also scored significantly poorer than group 2 on the MMSE (26.6 versus 28.0, $t = -2.223$, $p = 0.032$), the concept shifting test (58.3 versus 43.3, $t = 2.079$, $p = 0.045$), the letter digit substitution test (30.0 versus 38.6, $t = -2.736$, $p = 0.009$), the verbal learning test immediate recall (8.1 versus 10.5, $t = -3.274$, $p = 0.002$), and the verbal learning test delayed recall (5.4 versus 7.9, $t = -2.560$, $p = 0.015$). This suggests that at least some participants in group 3 were already in a pre-clinical phase of dementia at baseline.

At t_3, group 2 performed significantly lower than group 1 on the MMSE (26.3 versus 28.2, $t = -4.493$, $p < 0.001$), the Fluency task (18.3 versus 21.4 named animals, $t = -2.505$, $p = 0.015$) and the verbal learning test – delayed recall (7.6 versus 9.9 remembered words, $t = -3.696$, $p < 0.001$). Group 3 performed significantly poorer than the other two groups on all cognitive tests ($p < 0.05$), only the difference in MMSE score between groups 2 and 3 did not reach significance (24.8 versus 26.3, $t = 1.722$, $p < 0.093$).

3.2. Volumetric comparisons among the three groups

Fig. 2 shows the relative volumes of the brain structures for the three groups at t_3. All volumes were calculated as the sum

Table 1
Group characteristics

	Group 1: no decline (*n* = 35) Mean (S.D.) or %	Group 2: cognitive decline (*n* = 30) Mean (S.D.) or %	Group 3: dementia at t_9 (*n* = 9) Mean (S.D.) or %
t_0			
Age (years)	69.1 (7.7)	69.2 (8.1)	73.8 (4.3)
	Range 49.3–79.3	Range 50.0–81.0	Range 70.1–84.2
Female sex (%)	54.3%	46.7%	44.4%
Educational level (CBS)	2.5 (1.7)	2.3 (1.2)	2.3 (1.4)
MMSE	27.9 (1.6)	28.0 (1.8)	26.6 (1.3)
CST, subtest C (s)	44.6 (13.0)	43.3 (19.5)	58.3 (16.8)
Fluency (named animals)	21.9 (5.9)	21.1 (6.6)	18.0 (3.3)
LDST (items after 90 s)	39.8 (7.7)	38.6 (8.5)	30.0 (7.4)
Stroop, subtest 3 (s)	113.4 (25.0)	117.7 (26.3)	134.9 (28.7)
VLT immediate recall (words)	10.9 (2.8)	10.5 (1.8)	8.1 (2.3)
VLT delayed recall (words)	9.3 (2.7)	7.9 (2.5)	5.4 (2.7)
t_3			
Intracranial volume (cm^3)	1062.3 (142.9)	1069.1 (115.2)	1063.1 (110.3)
MMSE	28.2 (1.5)	26.3 (2.0)	24.8 (3.1)
CST, subtest C (s)	41.7 (13.5)	45.6 (12.1)	60.8 (12.5)
Fluency (named animals)	21.4 (4.6)	18.3 (5.5)	13.8 (3.4)
LDST (items after 90 s)	40.1 (7.8)	38.7 (9.8)	25.4 (9.3)
Stroop, subtest 3 (s)	118.2 (29.0)	128.9 (32.9)	161.0 (35.3)
VLT immediate recall (words)	11.5 (1.9)	10.8 (2.0)	7.7 (1.7)
VLT delayed recall (words)	9.9 (2.5)	7.6 (2.4)	4.6 (2.7)

Note: group 1 = participants with no cognitive decline in the three years prior to MRI and who did not develop dementia within six years after MRI (*n* = 35); group 2 = participants with significant cognitive decline who did not develop dementia (*n* = 30); group 3 = participants who developed dementia within six years after MRI; CBS = seven-point score for educational level (1 = elementary school; 7 = university) (Van den Brandt et al., 1990); MMSE = mini-mental state examination; CST = concept shifting test; LDST = letter digit substitution test; VLT = verbal learning test; t_0 = baseline; t_3 = three years after baseline.
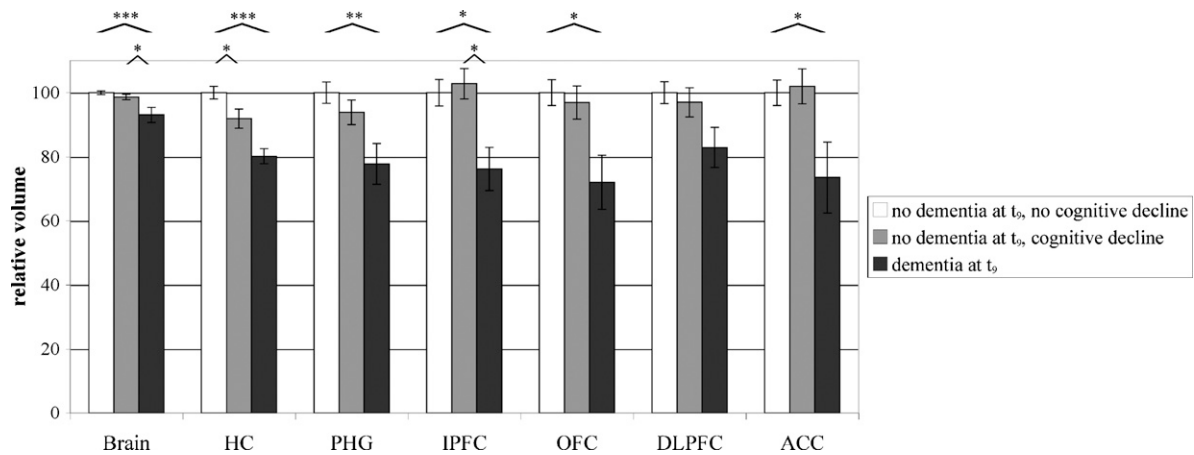
Fig. 2. Relative volumes of the brain structures for the three groups at t_3. The volumes indicate the sum of the left and right hemisphere regions of interest, after adjustment for intracranial volume. All volumes have been linearly transformed in such a way that the volumes of the cognitively healthy group were set at 100%. In this way, the differences between groups can be easily compared across brain structures. Error bars represent standard errors of the mean. Abbreviations: HC = hippocampus, PHG = parahippocampal gyrus, IPFC = inferior prefrontal cortex, OFC = orbital prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, ACC = anterior cingulate gyrus, t_9 = nine years after baseline. Significant differences between groups were analysed with GLM: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

of the left and right hemisphere. A comparison of volumes between groups 1 and 2 demonstrated a significantly smaller volume for group 2 in the hippocampus (6.8 versus 7.4 cm^3, $F = 6.722$, $p = 0.012$) but no significant volume differences in any of the other structures. When group 3 was compared to the other two groups, more differences were found. In most brain structures, the volume of group 3 was significantly smaller than the volume of group 1 ($p < 0.05$). The only structure that did not significantly differ between these groups was the dorsolateral PFC (23.9 versus 28.1 cm^3, $F = 2.646$, $p = 0.112$). In all brain structures, the volume of group 3 was substantially smaller than the volume of group 2. However, the differences between groups 3 and 2 were only significant in the inferior PFC (8.0 versus 10.7 cm^3, $F = 4.773$, $p = 0.036$). An interesting finding is that the difference between groups 2 and 3 was significantly larger in the PFC than in the MTL. We compared group differences between the total MTL volume and the total PFC volume and found a significantly larger group difference in the PFC ($F = 4.960$, $p = 0.032$).

4. Discussion

The aim of the present study was to investigate the relationship between PFC atrophy and the development of dementia. The first main finding was that PFC volume, especially the inferior PFC volume, was significantly smaller in participants who developed Alzheimer type dementia than in participants who showed cognitive decline but did not develop dementia. The second main finding was that PFC volume had a better predictive power in distinguishing between these two groups than MTL volume. The results demonstrated that PFC atrophy is highly associated with dementia. It is therefore not

only involved in the normal aging process (Raz et al., 2005; Tisserand et al., 2002), but also in the pathological aging process. Additionally, the results suggested that PFC atrophy that is based on anatomically correct volumetry might be a better predictor (i.e. biomarker) for dementia than MTL atrophy.

A few comments on the results of the current study can be made. Firstly, the hippocampus is the only structure that was significantly smaller in participants with cognitive decline (group 2) than in participants with no decline (group 1). This finding corresponds with previous research in which the hippocampus has been found to be associated with cognitive decline (Persson et al., 2006; Tisserand et al., 2004; Visser et al., 1999). However, the hippocampus was not significantly smaller in participants who developed dementia (group 3) when compared to those who showed cognitive decline (group 2). In fact, group differences between groups 2 and 3 did not reach statistical significance in most of the brain structures measured. This may be attributable to the small number of participants in group 3.

Secondly, participants in group 2 had low scores on the verbal learning test – delayed recall (memory test) at baseline and had relatively small hippocampi. This might be suggestive of the earliest stage of dementia. However, the participants of group 2 did not develop dementia within nine years after the baseline assessment. The chance that preclinically demented subjects were included in group 2 is therefore very small.

Thirdly, the medical profile of the nine participants who developed dementia was compatible with AD or mixed AD and vascular dementia (VaD). Therefore, we cannot uniquely attribute these results to AD. However, this does not imply that the results are therefore clinically less relevant. In fact, a mixed type of dementia is very common. It has even been

suggested that classifying dementia into AD and VaD may be incorrect given that vascular risk factors and lesions are very common in patients with AD (De la Torre, 2002). The uncertain classification of AD and VaD justifies that we included a mixed subtype of dementia.

Fourthly, we found that the difference in volume between groups 2 and 3 was larger in the IPFC than in the hippocampus. One might suggest that this is the result of selection bias. The original size of the IPFC (i.e. the size in early adulthood) could have been larger in group 2 than in group 3, and this could be responsible for our finding. However, in this study we adjusted all the volumes for intracranial volume. Besides, the intracranial volumes of the three groups were very similar (i.e. no significant difference). If we assume that intracranial volume reflects the original brain volume, the similar intracranial volumes suggest that group 2 did not have a larger mean IPFC than group 3 in early adulthood. Thus, it is unlikely that selection bias is responsible for our finding.

A unique aspect of the present study is that we measured the behavioral data longitudinally over a period of nine years. Earlier studies that focussed on prefrontal cortex degeneration in dementia (Salat et al., 1999, 2001) were cross-sectional. Salat et al. (1999, 2001) reported PFC atrophy in Alzheimer's disease and found that the degeneration was most prominent in the inferior PFC. This is in agreement with our findings. However, while Salat et al. found a decreased PFC volume in dementia, we found a smaller PFC volume in *preclinical* dementia. We could therefore conclude that PFC atrophy can be considered as a predictor of the disease. Another merit of our study is that we made a direct comparison between the predictive value of MTL atrophy and PFC atrophy, which has not been done before.

In conclusion, PFC atrophy was shown to be highly associated with dementia and even was a better predictor for dementia than MTL atrophy. This finding suggests that, in the search for diagnostic markers for dementia, PFC atrophy needs more attention.

Conflicts of interest

No conflicts of interest to declare by any of the authors.

Acknowledgements

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