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Post-Mortem 7.0-Tesla Magnetic Resonance Imaging of the Hippocampus during Normal Aging and in Neurodegenerative Dementias

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Abstract

Except for atrophy of the hippocampus no other lesions have been investigated in neurodegenerative dementia diseases. The present post-mortem study with additional 7.0-tesla magnetic resonance imaging investigates the incidence and the degree of the severity of the hippocampal atrophy and the incidence of hippocampal micro-bleeds and micro-infarcts.

Hippocampal atrophy is significantly more severe not only in Alzheimer's disease but also in frontotemporal lobar degeneration, compared normal age-related brains and other neurodegenerative diseases, such Lewy body disease, progressive supranuclear palsy and corticobasal degeneration. Cerebrovascular lesions are rare except for small bleeds in FTLD. The hippocampi in most of the neurodegenerative diseases seem to be protected from cerebrovascular involvement, in contrast to the overall high frequency of these lesions in the largest part of the hemispheric cerebral cortex.

Keywords: Post-mortem 7.0-tesla magnetic resonance imaging; Hippocampal atrophy; Hippocampal micro-bleeds; Hippocampal micro-infarcts; Normal brain aging; Alzheimer's disease; Frontotemporal lobar degeneration; Lewy body disease; Progressive supranuclear palsy; Corticobasal degeneration

Introduction

In vivo measurement of human hippocampal volume (HV) and shape with magnetic resonance imaging (MRI) has become an important element of neuroimaging research [1]. HVs are inversely correlated with age in older healthy persons [2]. Hippocampal atrophy (HA), as evidenced using MRI, is one of the most validated biomarkers of Alzheimer's disease (AD). However, its imperfect sensitivity and specificity have highlighted the need to improve the analysis of the MRI data [3]. HV as an index of AD in post--mortem MRI scans of brains in the Nun study is a better indicator than delayed memory measure [4]. Also faster HV loss is observed in the presence of the ApoE genotype epsilon4 and in decreased cerebrospinal fluid Abeta [5].

On MRI HA is as severe in fronto-temporal lobar degeneration (FTLD) as in AD [6,7]. On MRI HA in Lewy body disease (LBD) is found to be absent [8] or less important than in AD [9] and in Parkinson's disease [10]. However, when LBD is associated with AD-type pathology, the HA is more important [11]. MRI findings in progressive supranuclear palsy are mainly focused on midbrain atrophy and diffuse white matter changes. No specific references are found concerning hippocampal lesions [12,13]. In corticobasal degeneration (CBD) the MRI is mainly focused on the asymmetrical cortical atrophy and the white matter lesions. Hippocampal lesions are not specifically mentioned [14,15]. The present post-mortem 7.0-tesla MRI examines selectively the structural changes in the hippocampus during

normal aging and in different neurodegenerative dementia diseases.

Material and Methods

The examined post-mortem brains consisted of 34 normal ones and 107 with different neurodegenerative diseases. The normal brains were subdivided in those of 20 middle-aged with on average age of 43 (31-55) years and 14 elderly persons with average age of 75 (67-83) years. The demographic features of the different examined groups are labeled in (Table 1).

Table 1: *Demographic data of the different patient groups.*

Items	Amount	Age (SD)	Male (%)
Normal middle-aged	20	43 (31-55) yrs	50%
Normal elderly	14	75 (67-87) yrs	64%
Alzheimer's disease	45	78 (65-83) yrs	41%
Frontotemporal lobar degeneration	21	69 (63-75) yrs	59%
Lewy body disease	15	80 (74-87) yrs	73%
Progressive supranuclear palsy	20	67 (56-73) yrs	50%
Corticobasal degeneration	6	71 (67-75) yrs	33%

A previously obtained informed consent of the patients or from the nearest family allowed an autopsy for diagnostic and scientific purposes.

The brain tissue samples were acquired from the Lille Neuro-Bank of the Lille University that is part of the "Centres des Resources Biologiques" and acts as an institutional review board. The neuropathological diagnosis of "pure" neurogenerative diseases, without associated pathology, was made according a standard procedure. Several small samples of the cerebral cortex and of the hippocampus of one fresh cerebral hemisphere were taken for histochemical examination. The remaining brain was fixed in formalin and, after 3 weeks, samples were taken from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulate gyrus, the basal nucleus of Meynert, the amygdaloid body, the hippocampus, basal ganglia, mesencephalon, pons, medulla and cerebellum. Slides from paraffin-embedded sections were immunostained for protein tau, β-amyloid, alpha-synuclein, prion protein and TDP43.

A 7.0-tesla MRI Bruker BioSpin SA was used with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany), according to a previously described method [16]. Previous to the brain sampling, three up to six coronal sections of a cerebral hemisphere were submitted to SPIN ECHO T2 and T2* MRI sequences: frontal, central and parieto-occipital ones. The hippocampus was evaluated on the most representative section. The degree of HA was determined according to the classification of Scheltens in 4 grades [17,18]. Also the incidence of hippocampal micro-bleeds (HMBs) and micro-infarcts (HMIs) was evaluated as previously described for cortical hemispheric cortical micro-bleeds (CoMBs) and cortical micro-infarcts (CoMIs) [19]. Also the findings in middle-aged and normal elderly persons were mutually compared.

Univariate comparisons of unpaired groups were performed with the Fisher's exact test for categorical data. The non-parametric Mann-Whitney U test was used to compare continuous variables. The significance level, two-tailed, was set at ≤ 0.01 for significant and ≤ 0.001 for highly significant. Values set at ≤ 0.05 and more than > 0.01 were considered as marginal significant.

Results

When comparing the middle-aged with the elderly normal persons a non-significant increase of the HA and of the number of HMBs and HMIs was observed (Table 2). When comparing the age-related normal elderly brains to those with a neurodegenerative dementia disease only in AD and FTLD a very significant degree of HA was observed. No significant HA was found in the LBD, PSP and CBD, compared to the normal age-related brains. Only in FTLD a significant increase of HMBs was seen. HMIs were not significantly more frequent in the different neurodegenerative dementia brains compared to normal brains of the same age group (Table 3).

Table 2: *Comparison of the non-significant average incidence (standard deviation) of hippocampal lesions between middle-aged and elderly persons with a history of normal cognition.*

Items	Hippocampal atrophy	Cortical micro-bleeds	Cortical micro-infarcts
Aged 43 (31-55) years	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Aged 75 (67-83) years	0.4 (0.8)	0.4 (0.8)	0.1 (0.3)

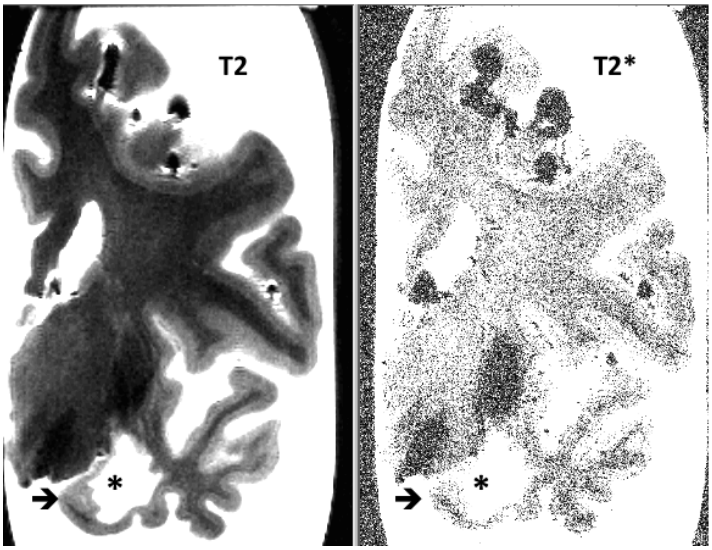
Table 3: *Comparison of the average incidence (standard deviation) of the hippocampal changes of age-controlled normal brains to those with different neurodegenerative dementia diseases.*

Items	Hippocampal atrophy	Cortical micro-bleeds	Cortical micro-infarcts
Alzheimer's disease	2.5 (1.1)***	0.4 (0.8)	0.1 (0.3)
Frontotemporal lobar degeneration	2.0 (1.0)***	1.3 (1.0)**	0.3 (0.1)
Lewy body disease	0.5 (0.7)	0.3 (0.6)	0.2 (0.4)
Progressive supranuclear palsy	0.4 (0.6)	0.5 (1.0)	0.0 (0.0)
Corticobasal degeneration	0.2 (0.4)	0.0 (0.0)	0.5 (0.8)
*** p value ≤ 0.001; ** p value ≤ 0.01.			

Discussion

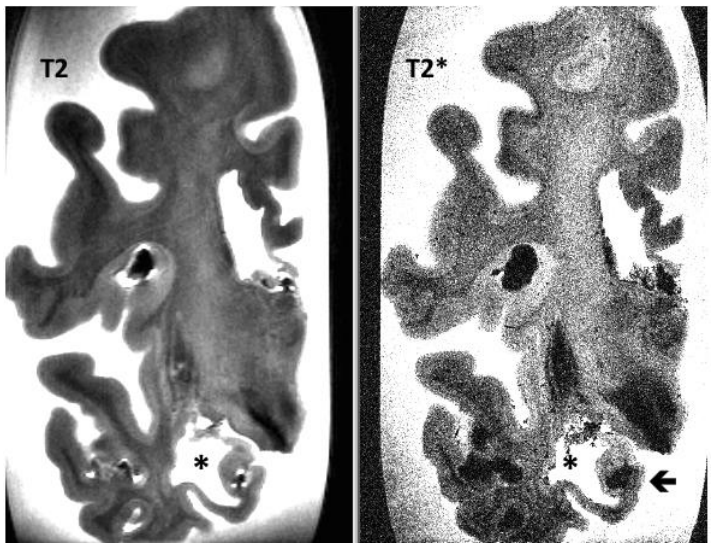
Visual assessment of medial temporal lobe atrophy correlates well with hippocampal volume [20]. There is a mild reduction in cerebral volumes with age, more marked in males [21]. In addition to some degree of brain shrinkage and increase of white changes, only a more or less similar increase of CoMBs is observed in middle-aged and elderly persons compared to young adults. The increase of CoMBs is probably due to mixed age-related cerebrovascular and neurodegenerative pathology [19,22] (Figures 1-2).

Figure 1: *T2 and T2* sequences of a coronal section of a cerebral hemisphere in Alzheimer's disease. The temporal horn is enlarged (*) with severe atrophy of the hippocampus (black arrow).*



In the present study HA is significantly severe in AD and FTLD compared to normal aging, LBD, PSP and CBD. The degree of HA alone does not allow differentiating AD from FTLD, as previously shown [6,7]. Post-mortem studies have not identified an association between ß-amyloid or tau and rates of HA in patients with AD. TDP-43 on the other hand appears as a potential factor related to increased rates of HA [23]. The average HV and ratio in AD is estimated to be reduced by 25% compared to 21% in mixed dementia and 11 % in vascular dementia [24]. There are also some differences in atrophy location in AD compared to other brain diseases [25]. CoMBs are significantly increased in AD brains, in particular when associated to cerebral amyloid angioaphy, in contrast to the hippocampus [26].

Figure 2: *T2 and T2* sequences of a coronal section of a cerebral hemisphere in frontotemporal lobe degenertion. The temporal horn is enlarged (*) with severe atrophy of the hippocampus and a small bleed (black arrow).*



The increase of HMBs in FTLD is more probably related to the severe neurodegenerative changes in the fronto-temporal regions rather than due to additional cerebro-vascular pathology [27]. The medial temporal lobe atrophy allows to differenciate AD from LBD [28]. CoMBs are frequent in LBD, in particular when associated to AD features [29,30]. This is in contrast to their low incidence in the hippocampus in pure LBD as well as pure AD.

MBs and MIs are restricted to the neurodegenerative changes of the brainstem and cerebellum in PSP. The hippocampus is not significantly affected [31]. Hemispheric CoMBs are increased in brains with CBD, in contrast to the hippocampus [32]. CoMIs are frequently observed in different neurodegenerative diseases, mainly in the mixed forms [33,34]. However, the hippocampus seems to be spared in the present study.

The involvement of hippocampus in neurodegenerative dementia diseases shows significant differences. Atrophy is only observed in AD and FTLD. Cerebrovascular lesions are rare except for small bleeds in FTLD. Most of the neurodegenerative diseases seem to be protected for cerebro-vascular participation, in

contrast to their overall frequent involvement.

Author Contributions

Jacques De Reuck has designed the study. Together with Florent Auger and Nicolas Durieux he performed the MRI examinations. Claude-Alain Maurage and Vincent Deramecourt performed the macroscopic and histological examinations of the brains. Charlotte Cordonnier, Florence Pasquier, Didier Leys and Regis Bordet were responsible for clinical evaluation during life.

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Competing Interests

The authors have declared that no competing interests exist.

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