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Brain atrophy parameters of very old subjects in a population – based sample with and without dementia syndrome

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Abstract Atrophy parameters of the brain vary with age in healthy subjects. The aim of the study was to determine the range of atrophy parameters in subjects with very old age. Population-based data are especially necessary in order to evaluate atrophy parameters of healthy old persons in clinical settings and for the diagnosis of dementia diseases. 254 subjects in a population-based sample were investigated by a cranial computerized tomography (cCT). Age ranged from 70 to 99, 78 were 80–89 years old and 43 over 90 years of age; 24 demented subjects were diagnosed according to DSM-III-R. A planimetric analysis of the extracerebral CSF-space (ECSF) and relative area of the ventricles (VBR) was performed. VBR and ECSF were used as primary atrophy parameters. The VBR, ECSF and other structural brain parameters for subjects of very old age are described after exclusion of dementia cases according to clinical diagnosis. A statistically significant age effect could be demonstrated as well as a dementia effect for the younger age groups (70–89). No difference in the atrophy parameters between the diagnostic groups, however, were found for the oldest groups (90 and older); for the very old subjects the scores of demented and non-demented participants were entirely within the same range. The age effect on atrophy parameters in non-demented subjects in very old age reaches the range of atrophy parameters, which is found in dementia. The question remains wheather the reason for this is a benign senescent brain atrophy or whether the amount of atrophic changes in very old age may explain the enhanced vulnerability for the development of dementia syndromes in very old age and the steeply increasing incidence of dementia or whether there is an incipient brain atrophy in more or less all very old subject and they will develop dementia if they do not die beforehand.

Key words Dementia · Old age · Computer tomography · Atrophy

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Introduction

Brain atrophy in old subjects who are non-demented is well-documented (Wahlund et al. 1990, Breteler et al. 1994). The existing data in the literature document a large increase in parameters of brain atrophy like ventricle brain ratio (VBR) from 70–79 to 80–89 years, varying between 17 and 22 % (Barron et al. 1976, Earnest et al. 1979, Jocoby et al. 1980). The existing data on the 10th decade, however, rest on very few subjects, not recruited in population-based samples (Earnest et al. 1979).

Often normative data for brain imaging research have been collected by investigating clinical samples of subjects, who were diagnosed as having no brain disease. But these cCT data may be biased by the clinical signs and symptoms leading to the investigation by cCT as well as by the exclusion of subjects with apparently non-normal findings. Valid normative data can be best obtained in a population-based study.

First, for this analysis the dementia diagnosis is important in order to exclude the demented subjects from the normal control sample. The diagnosis is relevant especially in very old age, because of the steep increase of dementia prevalence from 70 to 95 years (Jorm et al. 1987). By means of a standardized psychiatric investigation the dementia cases are identified in the current sample.

Normative data are essential a) for the diagnostic evaluation of dementia and b) for helping to understand the question whether brain atrophy phenomena in old age are depending on normal age-related processes or on dementia diseases. Therefore the aim of the study

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was to determine, to what extent aging affects the atrophy parameters of the brain of non-demented subjects in very old age, i.e., in the 9th and 10th decade. In case there is a continuous increase of the atrophy parameters with age, the parameters of brain atrophy may reach the range of atrophy, which is found in dementia or alternatively the difference between subjects with dementia and non-demented elderly may remain constant over the age range.

Methods

As part of an epidemiological study (BASE, Baltes et al. 1999) 254 subjects were investigated by cCT scan. BASE subjects were drawn at random from the Berlin registration office. Within the age group of 70–89 years there were N=211 subjects; in the age group 90 years and older were N=43 subjects. Men (N=145) had a mean age of 82.2 (sd 8.2) and women (N=109) 81.1 (sd 7.1) years. There was some selectivity in the sample because multimorbid very old women more often refused to take part in this rather technical investigation. In comparison with the Berlin census data the final cCT population differed only with respect to a few parameters like education and financial income, i. e., the cCT sample had more middle-level education (census 18.8 % males, 19.9 % females vs. current sample 33.9 % males and 34 % females) and more persons with higher income (more than 2000 DM/month: 35.3 % males and 17.3 % females, vs. current sample 65.9 % males and 24.7 % females).

Research psychiatrists investigated all subjects, applying the Geriatric Mental State-A interview and History and Aetiology Schedule (Copeland et al. 1990), and using the DSM-III-R dementia criteria (290.00). N=24 subjects received a dementia diagnosis (see Table 2) according to a clinical evaluation by research psychiatrists and a consensus conference together with the geriatric colleagues, who performed the somatic investigation. No attempt was made to further specify the dementia diagnosis especially with respect to vascular dementia, because many of the very old subjects live alone and no valid information of a closely related person could be obtained. Severe dementia syndrome cases had to be excluded because of inability to give valid consent. No other selectivity effects as noted above were found for the demented subjects who participated in the cCT investigation compared to those who refused. There were more female dementia cases without cCT (63.6 %) compared to the 41.7 % who could be included in the study. Within this sample demented subjects were rare up to 90 years of age – therefore the age groups were combined in order to have an approximately equal number of demented subjects for the statistical comparisons. This resulted in a contrast of subjects 70 to 89 and 90+ years. In the age group 70–89 years (N=211) there were 15 dementia cases, in the age group 90+ years (N=43) remained however only 8 dementia cases.

Several radiological investigations are available for assessing atrophy parameters of the brain, one of these is the cCT. One reason for the decision to use the cCT is economics. Normative data are necessary for dementia evaluation in many sites, where MRI is often not available. Additionally administering the MRI poses some difficulty because of frequent claustrophobic anxiety, etc.

After complete explanation of the study to the subjects, written informed consent was obtained. The cCT scan was performed using a Siemens Somatom DRH for all subjects and the raw data were stored. The slices were planimetrically analyzed by a physician who was blind for diagnosis, age, and sex of the subjects (W. R.) applying the VAC software for automatic outlining homogenous regions in cCT (Siemens Somatom).

VBR and extra-cerebral cerebrospinal fluid (ECSF) space were chosen as primary parameters. The main reason for this is to compare the data with the existing literature. Definitions: a) ventricle brain ratio (ventricle area related to intracranial area, VBR); c) brain area related to intracranial area (brain ratio); d) subarachnoidal CSF area related to intracranial area (ECSF ratio) and to brain area (ECBR). The automatic planimetric analysis resulted in identical values compared with a high-lighting technique with a manual delineation of the ventricle at a 0.5 cm distance and cut off values of –5 and 22 HU. The density of the white matter was measured in two circular regions of interest of 2.25 cm^2 in the left and right frontal white matter.

In the study only a limited CT investigation could be done because of restraints of the ethical approval for a population-based investigation. Only those slices were investigated which matches the Matsui anatomical atlas (Matsui et al. 1978) level 8 and 9 (15-degree tilt). Within these levels are depicted the basal ganglia and the cortical language areas – Broca area in the frontal lobe and Wernicke area in the temporal lobe. In some subjects for one of the levels no scan could be analyzed, therefore the groups regarding the two slices have slightly different numbers of subjects (see Table 2). The interrater reliability of the assessment of the atrophy parameters was high r=0.99.

Results

The age effect on atrophy parameters was found to be large – as shown in Table 1, which presents normative data for the non demented subjects of BASE. The correlation between age and the atrophy parameters were statistically significant for the non-demented subjects (VBR $r=0.40$, $p < 0.05$; brain ratio $r=0.48$, $p < 0.05$; ECSF $r=0.41$, $p < 0.05$) but not statistically significant for the demented subjects.

A two-way ANOVA was performed with the factors age (young-old and old-old) and dementia. The ANOVA results are described subsequently for the level Matsui 8 and 9. (Table 2): For the VBR level Matsui 8 there is a statistically significant interaction between age and diagnosis ($F(1,205)=5.24$, $p < 0.025$), with a higher dementia effect in the younger group compared with the old group (see Table 2, Fig. 1). No single effect reaches the significance level. Also for the brain ratio only the interaction term is significant ($F(1,205)=4.00$, $p < 0.05$). The ECSF ratio shows a significant age effect ($F(1,205)=7.78$, $p < 0.01$). For this parameter the interaction term is not significant ($p=0.37$). For the density parameters no statistical significant group effect or interaction was found.

For level Matsui 9 the VBR demonstrates a significant dementia effect ($F(1,184)=7.89$, $p < 0.01$) and a significant interaction term ($F(1,184)=3.97$, $p < 0.05$). The

Tab. 1 Ventricle Brain Ratio (VBR) and ratio of external CSF space to brain area (ECBR) in 6 age-groups of non-demented subjects for slices Matsui 8/ Matsui 9 (15°) sd: standard deviation

Age group	70–74	75–79	80–84	85–89	90–94	95+
VBR	0.10/0.08	0.12/0.10	0.13/0.11	0.14/0.10	0.15/0.12	0.14/0.13
sd	0.03/0.03	0.04/0.03	0.04/0.03	0.04/0.03	0.04/0.03	0.04/0.04
ECBR	0.10/0.10	0.13/0.12	0.13/0.13	0.15/0.14	0.17/0.16	0.18/0.16
sd	0.05/0.05	0.05/0.05	0.06/0.05	0.06/0.06	0.05/0.05	0.06/0.05
N	46/43	44/48	41/36	37/28	19/14	19/16

Tab. 2 Age and dementia effect: For two levels according to Masui Brain Atlas (8 and 9 at 15°) demented and non-demented subjects were compared for 4 parameters. Post hoc statistically significant comparisons are noted as letters, groups are identified by letters a to d; the group to which a statistical significant difference occurred is named by the letter (n. s.: not statistically significant)

Parameter	70–89 years (post hoc comparisons) control (a)	demented (b)	> 90 years control (c)	demented (d)	Statistics: Single effect	Interaction
Matsui 8						
VBR	0.120 (b,c)	0.159	0.144	0.140	n. s.	$p < 0.025$
sd	0.038	0.038	0.038	0.043		
Brain ratio	0.784 (b,c)	0.727	0.729	0.730	n. s.	$p < 0.05$
sd	0.060	0.062	0.054	0.045		
ECSF ratio	0.096 (c)	0.114	0.127	0.130	age $p < 0.01$	n. s.
sd	0.034	0.035	0.035	0.026		
Density	33.4	33.7	33.6	34.7	n. s.	n. s.
sd	2.73	2.58	2.78	3.03		
N	155	13	30	8		
Matsui 9						
VBR	0.094 (b,c,d)	0.134	0.124	0.131	dementia	$p < 0.05$
sd	0.030	0.040	0.036	0.032	$p < 0.01$	
Brain ratio	0.811 (b,c,d)	0.739	0.756	0.741	dementia	$p < 0.10$
sd	0.053	0.067	0.060	0.034	$p < 0.005$	
ECSF ratio	0.095 (b,c)	0.127	0.120	0.128	dementia	n. s.
sd	0.033	0.035	0.034	0.017	$p < 0.025$	
Density	33.8	33.3	34.7	34.9	n. s.	n. s.
sd	3.02	3.78	3.37	1.67		
N	145	10	22	8		

VBR ventricle brain ratio; ventricle area related to intracranial area; *Brain ratio* brain area related to intracranial area; *ECSF ratio* subarachnoidal cerebrospinal-fluid area related to intracranial area; *Density* density of frontal white matter CT-paramters of cerebral atrophy for demented and non-demented subjects (Houndsfield units)

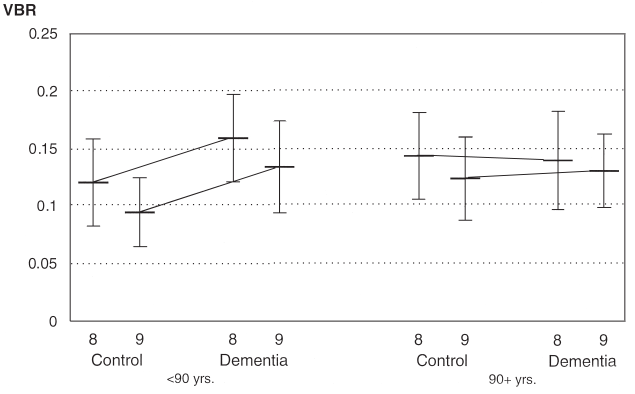

Fig. 1 Age effect and dementia effect on the ventricle brain ratio – separated for the Matsui 8 and 9 level of cCT. The age effect on atrophy parameters reaches the range of the demented subjects. Only for subjects younger than 90 years there is a difference between non-demented and demented subjects.

same was found for the brain ratio ($F(1,184)=9.15$, $p < 0.005$) with a marginal significant interaction term ($F(1,184)=3.80$, $p=0.053$). A dementia effect ($F(1,184)=5.34$, $p < 0.025$) could be also found for the ECSF ratio on this level.

The significant interaction between the age and dementia effects can be related at first to larger ventricles and external CSF space of the older non-demented subjects. Comparing the age groups for the VBR the following effect sizes were obtained (pooled): comparison of the young and old non-demented subjects, a difference of 0.63 standard deviations (sd) was found in level Matsui 8 and 0.97 sd in level Matsui 9.

The ECSF ratio in the 9th decade was 18 % larger than in the 8th, and from the 9th to the 10th decade an increase of 17 % was calculated. The effect size of the difference was 0.52 sd for the 8th to 9th decade and 0.55 sd for the 9th to 10th decade (pooled sd).

The dementia effect is again reported first for the Matsui 8 level; for the younger age group (70–89) there is a difference between the demented and non-demented subjects in two of the three atrophy parameters (see Table 2), with the exception of the ECSF ratio. In contrast to this the atrophy parameters are practically identical for the older age (90+, see Table 1). The effect size for the dementia effect was quite high in the younger group: demented-control young, effect size 1.03 sd (Matsui 8), 1.30 sd (Matsui 9); however, the effects sizes were very small for the comparison demented versus control in old age, effect size –0.10 sd (Matsui 8), 0.20 sd (Matsui 9). No statistically significant effect of the density parameter was found.

In order to check whether the severity of dementia of the two age groups is different, the MMSE was compared. The dementia cases were of mild severity and no statistical difference was found: young demented 21.79 (sd 5.45) and old demented 21.43 (sd 3.10). For non-demented control subjects the correlation between VBR and MMSE was statistically significant, however explaining only a small proportion of the variance: $r=-0.29$, $p < 0.001$. The corresponding correlation for the ECSF ratio was $r=-0.36$, $p < 0.001$.

Discussion

The age effect on parameters of brain atrophy in non-demented subjects appears to be quite large. The ratio of the ventricle to brain area in the oldest non-demented subjects was found to be more than one – up to almost two – standard deviations higher than in the youngest

age group (see Table 1). The age effect in the very old subjects is even somewhat lower than the data reported in the literature, which, in contrast to this study, rely, however, on only very few subjects.

One of the main findings of the study is a statistically significant interaction of the age and dementia effect, i. e., the lack of a difference of atrophy parameters between demented and non-demented very old subjects (90 years and older) compared with the statistically significant difference in the younger sample (see Fig. 1). In the oldest age group (90+) the two diagnostic groups, demented and non-demented subjects, demonstrate the same range of cerebral atrophy as demonstrated by the VBR. Atrophy parameters are generally found to be higher in demented subjects compared to age-matched controls (Jacoby et al. 1980, Gado et al. 1982, Bradshaw et al. 1983, Ball et al. 1985, Pfefferbaum et al. 1990, DeCarli et al. 1996). This is true for quantitative analyses of linear parameters, area size as well as volumetric parameters (George et al. 1983, Turkheimer et al. 1984, Creasey et al. 1986). Whereas there is quite a consistent statistical difference between the diagnostic groups at younger age, no comparison between the diagnostic groups for the old subjects approaches significance (see Fig. 1). The result is especially valid because not a clinical sample but a population-based sample has been studied. Unlike clinical studies sampling was not biased by medical indication to obtain the cCT scan in each individual. Therefore the results may be generalized to old-age dementia syndrome and the normal age effect.

Atrophic processes of the brain are assessed with high precision by cranial computerized tomography (Fazekas et al. 1989). No specific advantage of the MRI for assessing general atrophy has been reported (George et al. 1983, Turkheimer et al. 1984, Creasey et al. 1986), but MRI allows for analysis of regional atrophy like in the hippocampal area (see below). By comparing the ventricle brain ratio (VBR) of demented and control persons the effect sizes (in units of standard deviation) of the atrophy parameters revealed a large range of 0.46 to 2.55 (Diff/sd) in the published data, i. e., the difference between the diagnostic groups varied from half a standard deviation (sd) to two and a half sd's. Brinkmann (Brinkman et al. 1981) reported a difference with an effect size of 0.46 sd, Jacoby (Jacoby et al. 1980 a, b) 1.64 sd and Colgan (Colgan et al. 1986) 2.24 sd. For the lateral ventricles Eslinger (Eslinger et al. 1984) reported an effect size of 2.55 sd. Our data of 1.09 to 1.30 sd difference for the young group is in concordance with the data of the literature for the younger subjects. There seems to be a large overlap between the atrophy parameters of demented and non-demented younger subjects. Older studies on visual inspection of cCT found 15 % to 27 % normal cCT in demented subjects (Jacoby et al. 1980, Kohlmeyer 1982). The high variance of atrophy parameters in healthy control subjects may be one of the reasons that 40 % of demented persons scored within the range of normal subjects (Hubbard et al. 1981).

In contrast to a more general atrophy in dementia cases, a more selective atrophy related to Alzheimer dementia and senile dementia of Alzheimer type has been described in the literature – e. g., hippocampal atrophy (Gabo et al. 1982, Turkheimer et al. 1984, George et al. 1990, Kesslak et al. 1991, Ikeda et al. 1994) or atrophy of areas of the medial temporal lobe (Jobst et al. 1992, Wyper et al. 1993). These cannot be differentiated by the methods used in this study. The question should be addressed in further studies as to whether hippocampal or entorhinal atrophy is valid for the diagnosis of dementia in very old subjects aged 90 years and older.

Severely demented subjects were not allowed to participate in BASE due to ethical reasons regarding the informed consent. This argument, however, holds for the young and old demented and cannot explain the data. It could, furthermore, be discussed that the older demented subjects might represent a population of milder dementia and that the difference in cCT parameters is therefore diminished. However, the severity of dementia in the older group was the same as in the younger group, according to clinical evaluation and the MMSE score. The dementia syndromes were of mild to moderate severity with a MMSE of about 21 points (Reischies et al. 1997). Thus, severity of dementia cannot explain the results.

There was no ceiling effect for the atrophy parameters of the demented subjects. To the contrary the highest ventricle brain ratio values were from the non-demented subjects in 8 cases and from the demented subjects in only 3 cases. One of the possible explanations may be that demented subjects will not reach the extreme extent of cerebral atrophy because they may die from other causes beforehand. The literature report of the cCT of the oldest centennarian person also demonstrates considerable signs of brain atrophy (Ritchie 1995).

It can be argued that the conclusion with respect of the interaction of age and dementia effect rests on very few, very old demented subjects. However a relatively large number of non-demented control subjects from a population-based study were investigated in this study. The VBR data of old demented subjects are well within the range of those cases reported in the literature (Burns et al. 1991). It appears clearly that the atrophy parameters of the non-demented control subjects of our study are in the range of atrophy parameters which are found in dementia. Thus, although there are few epidemiologically verified dementia cases within this sample, the demonstration of the same range of atrophy scores is especially valuable because the sample is population-based. Certainly, confirmation of the data in a sample of more very old dementia subjects, drawn from a population-based study, is needed.

One hypothesis which can explain the data is that there are two atrophy processes: one age-related benign senescent brain atrophy, which is benign with respect to the association with dementia syndrome and a second, dementia-related atrophy of the brain (see Wahlund et al. 1990). The second hypothesis is that the increase in

atrophy explains the vulnerability of the brains of very old persons with regard to dementia and delirium. It may explain the increase in incidence of dementia diseases, in the course of which rapidly progressive neuronal dysfunction and subsequent neuronal loss might lead more easily to a clinical deterioration of brain function for very old persons (see Breteler et al. 1994). The adverse effects of an accumulation of the Aß-peptide within the brain may be one reason of this general atrophic process. A third position is that the atrophy belongs to an aging process which will lead to dementia in all subjects if they do not die beforehand (Barron et al. 1976).

It can be seen as corroborating evidence for our finding that in brain autopsy studies in very old demented subjects there was also no significantly larger degree of neuronal loss in dementia compared to control persons of the same age (Mountjoy et al. 1983). Taken together these data with our results indicate that aging of the brain and dementing illness may interact and the high incidence of dementia in old age may depend on the preceding age effects – which are not specific for a specific dementia disease (Reischies et al. 1998). Furthermore, because of the already extensive age effect on the brain, in very old age only mild effects of a dementing illness may be sufficient for the clinical presentation of a dementia syndrome. For the diagnosis of dementia the assessment of global atrophy is clearly not helpful in very old age, according to our data. Future research must evaluate the vulnerability effect and the relation of ventricular and external atrophy to mediotemporal atrophy in very old age.

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