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Brief communication

No disease in the brain of a 115-year-old woman

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Abstract

Are there limits to the duration of high quality of life? Are there limits to healthy life for a human brain? We have had the opportunity to evaluate the performance of a 112–113-year-old woman and perform full pathological examination of her body immediately after death at the age of 115. The psychological tests revealed that her general performance was above average of healthy adults of 60–75 years. The pathological observations revealed almost no atherosclerotic changes throughout the body. In the brain almost no beta-amyloid plaques or vascular changes were found and only slight accumulation of hyperphosphorylated tau protein with a Braak-stage 2. Counts of the number of locus coeruleus neurons corresponded with the number of neurons found in the brains of healthy people of 60–80 years old.

Our observations indicate that the limits of human cognitive function extends far beyond the range that is currently enjoyed by most individuals and that brain disease, even in supercentanarians, is not inevitable.

Keywords: Atherosclerosis; Supercentenarian; Neurodegeneration; Tau; Locus coeruleus

1. Introduction

At the age of 111 a woman, who had donated her body to science at the age of 82, contacted the University of Groningen questioning if her body would still be of any use. We met a very alert attentive lady prepared to undergo neuropsychological examinations in which she performed better than the average 60–75-year-old adult. She remained alert until she died at the age of 115, being the world's oldest woman. Immediately after her death pathological examination at Groningen University showed almost no atherosclerotic changes in her body.

Our observations suggest that, in contrast to general belief, the limits of human cognitive function may extend far beyond the range that is currently enjoyed by most individuals, and that improvements in preventing brain disorders of aging may yield substantial long-term benefits.

2. Patient and methods

2.1. Case report

In 1972, at the age of 82, a woman (1890–2005) living in the province of Drenthe in The Netherlands sent a written consent to donate her body after death to the University in Groningen. In 2001, at the age of 111, she inquired whether her frail body, after death, was still useful for scientific research or teaching purposes. This led to a visit to her. She appeared to be an alert and assertive lady, full of interest in the world around her, including national and international politics and sports. Her eyesight was very poor, but she listened to the news on the radio every hour. She was able to

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tell us enthousiastically about her life from around the year 1900 until the present, including her positive and negative experiences.

At birth she weighed a mere 1600 g. Her mother expected her to die and did not take an interest in her. Her grandmother, however, took care of her, which was the reason that she survived. At five years of age she attended school, but immediately became ill, so it was decided that she should not attend school anymore. Her father, a school teacher, taught her at home. At 18 years of age she became a teacher herself. She left home when she was 47, married at 49 and did not bear children. She became a widow at 69 and remained self-supporting until she was 105. Mainly due to poor eye-sight she moved to a residential care home. Her mother died at the age of 100 years.

We explained to her that, in contrast to what she thought, we were very interested in her remains after death, especially because she was so old. She was very enthusiastic about her being important for science. At a later visit we asked her whether she was prepared to undergo a neuropsychological assessment, which she was very happy to submit herself to. After explaining to her what the implications of later neuropathological investigations might be, she was also very proud that her body was so valuable for studies on the neurobiology of aging.

2.2. Neuropsychological examination

The first assessment took place November 2002, in two sessions 1 week apart, when she was 112 years and 5 months old and another assessment in May 2004 when she was 113 years and 10 months old. The tests were administered in her living room by an experienced test assistant. Because of her poor eyesight, testing was limited to tests which did not require visual input or visual guidance during output. In 2002 she reported feeling well when tested but in 2004 she complained of poor sleep the night before. Unfortunately she refused to make an additional appointment to complete the last test, so that less test results are available for that occasion.

Table 1
Summary of the neuropsychological examination

Test domain	Specific test	Test date	
		November 2002	May 2004
Dementia screening	Mini mental state examination[a] (without visual items; max. = 27)	27	26
	Cognitive screening test[b] (max. = 20)	20	20
Attention	Digits forward (WAIS)	Score 6 Span: 5 digits (6th decile 55–65 years)	Score 5 Span: 5 digits
Working memory	Digit backwards (WAIS)[c]	Score: 6 Span: 4 digits (6th decile 55–65 years)	Score 2 Span: 2 digits
	Serial sevens[d]	4 errors (in complete series)	3 errors (stuck halfway; test terminated)
Verbal reasoning	Similarities subtest of the Groninger intelligence test[e]	>16 (7th decile 60–75 years)	not administered
Retrieval from semantic memory	Word fluency (1 min) animals[e]	15 (5th decile 60–75 years)	16 (5th decile 60–75 years)
	Word fluency (1 min) professions[e]	14 (6th decile 60–75 years)	10 (2th decile 60–75 years) (some preservation)
Mental arithmetic	Addition, subtraction, multiplication, division	Errorless and fast except division	A few small errors
Verbal learning and retention	Auditory free recall: 8-words test from the Amsterdam Dementia Screening Battery[f]	Immediate recall: 24 (50th percentile 91–95 years) Learning curve: 3-3-5-6-7 Delayed recall: 4 (50th percentile 91–95 years) Recognition: 100%	Test terminated because she felt too tired
	Story recall[g]	Immediate recall: 11 (4th decile 45–65 years) Delayed recall: 11 (4th decile 45–65 years)	Immediate recall: 11 (4th decile 45–65 years) Delayed recall: 8 (2th decile 45–65 years)
Tactile object recognition	Tactile naming test, left and right hand[g]	All 26 objects correct fast without any doubt	25 correct objects moderately fast

[a] Folstein, Folstein and McHugh, 1975.
[b] De Graaf, Deelman, B.G., 1991. Cognitieve Screening Test, Handleiding. Swets and Zeitlinger, Lisse, The Netherlands.
[c] Wechsler Adult Intelligence Scales (Dutch version).
[d] Strub, R.L., Black, F.W., 2000. The Mental Status Examination in Neurology, 4th ed. Davis: Philadelphia.
[e] Luteijn, F., van der Ploeg, F.A.E., 1982. Groninger Intelligentie Test, Handleiding, Swets and Zeitlinger: Lisse, The Netherlands.
[f] Lindeboom, J., Jonker, C., 1988. Amsterdamse Dementie Screeningstest, Swets and Zeitlinger: Lisse, The Netherlands.
[g] Lezak, M., 2004. Neuropsychological Assessment 4th ed. Oxford University Press: Oxford.

2.3. Post-mortem examination

The woman died in the early morning (2.00 am 30 August 2005). On the evening of her death, the director of the residential care home informed the last author that her death was near. We were able to transfer her body 2 h after her death to the dissection room of the Dept. of Anatomy, where autopsy was performed immediately after arrival of the body. During the autopsy, the brain was separately perfused through the carotid arteries with a 4% paraformaldehyde in 0.1 M Phosphate buffer (pH 7.4). From all the main organs, as well as from the aorta samples were snap frozen.

Special attention was given to the brain. After further immersion fixation for 1 week, the brainstem together with the cerebellum was removed by transsection perpendicular to the long axis of the brainstem at the level of the superior colliculus. After removal of the cerebellum, the brainstem was transversely lamellated in slices with a thickness of 4 mm. The cerebellum was lamellated sagitally. The hemispheres and midbrain were sectioned in the frontal plane using standardized neuropathological landmarks.

The left side of the brain stem, cerebellum, midbrain and hemisphere were used for routine paraffin embedding. From the brainstem 17 tissue blocks were made, five from the cerebellum and fifteen from the left hemisphere and midbrain. From these blocks, which have a maximal size of 3.5 cm × 2.5 cm, fifteen 5 μm thick sections were cut and stained for haematoxilin and eosin (HE), Kluver-Barrera (KB), Methanamine-Silver (MS), Servier-Munger (SM), glial fibrillary acidic protein (GFAP, polyclonal, DAKO 1:800), beta-amyloid (6F/3D, DAKO, 1:400), ubiquitin (polyclonal, DAKO, 1:100), alpha-synuclein (KM51, Novo-castra, 1:40) and TAU (AT8, Innogenetics, 1:20).

HE sections were used for the evaluation of neuronal loss, spongiosis and the presence of dystrophic neurons; KB for demyelination, MS for plaques, SM for neuronal inclusions, GFAP for gliosis, beta-amyloid for deposition in plaques or vessel walls, ubiquitin and alpha-synuclein for neuronal and glial cell inclusions, AT8 for neurofibrillar tangles (NFT's), other neuronal tau or glial cell inclusions (GCIs).

The right side was frozen after cryoprotection in sucrose 25%. 20 Nissl stained 50 μm thick brainstem sections were investigated for the number of neuromelanin containing neurons in the locus coeruleus. The total countings were corrected using the Abercrombie correction formula for split cell error. Two independent countings were performed by two of the authors (E.B. and J.K.).

3. Results

3.1. Neuropsychological examination

Test results are summarized in Table 1. These results led to the following conclusions.

Orientation: On both occasions we found (near) maximum performance on screening tests for dementia which indicates that orientation in time and place and retrieval of general knowledge were unimpaired.

With regard to attention and working memory, attention span was normal, approximately average for persons aged

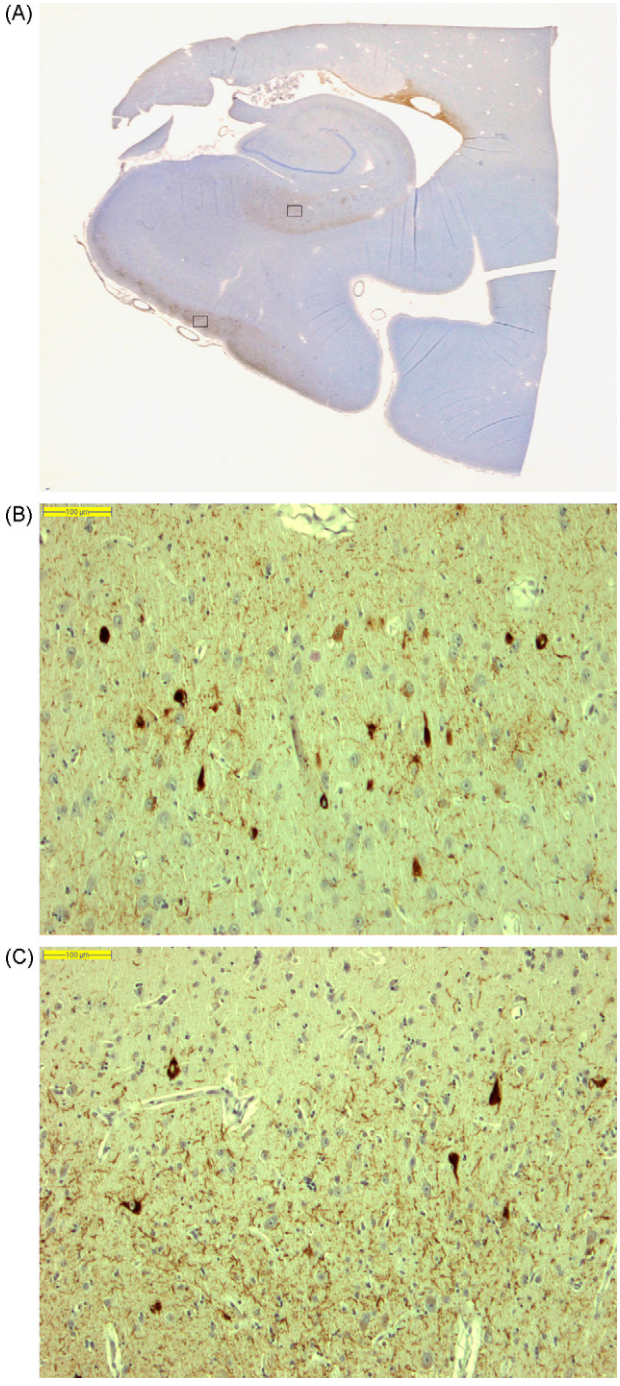

Fig. 1. (A) An overview of the hippocampal complex stained for hyperphosphorylated tau protein (AT8). Note that there is some staining in the subiculum and the entorhinal cortex, which are shown in more detail in (B) and (C), respectively. Neurofibrillary tangles or tau-positive neuropil was not found in the temporal isocortex.

60–75, but some central executive limitations of working memory were found, especially on the second occasion, as indicated by the limited digit span backward, the poor serial sevens, the small errors in mental arithmetic and the perseverations on the word fluency test. Performance of reasoning and application of cognitive skills was above average of healthy adults of 60–75 years on the first occasion. On the second occasion, when she was almost 114, performance was slightly impaired but was still within the normal range for healthy older adults. Acquisition and delayed recall of verbal information were unimpaired on the first occasion, at an approximately average level for healthy persons half her age. On the second occasion, performance was slightly impaired but still within normal range for healthy older adults.

3.2. Post-mortem examination

The autopsy revealed a 7 cm diameter tumor in the cardiac part of the stomach, which had expanded through all stomach layers and which was partly ulcerated. There were multiple metastases in liver and kidney. There was also a tumor in the left axilla, which, after microscopy, appeared to be a metastasis of a ductular breast carcinoma, for which she had surgery in 1990 when she was 100 years old. There were only very limited signs of atherosclerosis, a few emphysematous changes in the lungs, and the myocard showed no abnormalities. Cause of death was the metastasized adenocarcinoma of the stomach.

In general in the brain no plaques were found in the Methanamine-Silver staining and beta-amyloid depositions were not observed. Kluver-Barrera staining showed no demyelination, and Servier-Munger staining showed normal axonal densities. In both the Servier-Munger and ubiquitin stains basically the same pattern of neuronal inclusions was found as in the TAU (AT8) staining (Fig. 1). Therefore, in Table 2 only the results for the haematoxilin and eosin and TAU (AT8) stains are listed. Lewy bodies or glial cell inclusions were not observed.

The cell counts of the neuromelanin cells in the locus coeruleus by two different individuals resulted in almost identical numbers of cells, i.e. 16,736 and 16,390 cells after Abercrombie correction (Fig. 2).

Table 2
Summary of the neuropathological examination

Region	H&E	AT8
Frontal cortex, BA10	Slight atrophy in the white matter, no obvious neuronal cell loss, no spongiosis	0 NFT, only a sporadic positive dendrite
Temporal cortex, BA21/22	Slight atrophy in the white matter, no obvious neuronal cell loss, no spongiosis	1 NFT and a few dendrites
Gyrus cinguli + adjoining motor gyrus, BA24	Less atrophic than the frontal and temporal cortex	1 NFT and a few dendrites
Parietal cortex, BA7	Less atrophic than the frontal and temporal cortex; some dystrophic neurons in layer 3	2 NFT's and a few dendrites
Occipital cortex, BA17	No real atrophy	0 NFT, only a few dendrites
Amygdala	Minimal atrophy, no spongiosis, no gliosis, only a few dystrophic neurons	Several NFT's in the corticomedial amygdaloid nucleus, only some NFT's in the basolateral nucleus
Hippocampal complex	Minimal atrophy, no spongiosis, no gliosis, only a few dystrophic neurons	In the (pre)subiculum, entorhinal and transentorhinal cortex more tau-deposition; stage 2 according to Braak and Braak (1995); Fig. 1
Ncl Ruber	Cell rich, no atrophy, only a few dystrophic neurons (total of 3 sections)	0 NFT, only a sporadic positive dendrite
Substantia nigra	Cell rich, no atrophy, only a few remnants of degraded neurons, macrophages with phagocytosed neuromelanin. 1 Lewy body (total of 4 sections)	4 NFT's, a few dendrites
Periaqueductal gray	Normal aspect (2 sections)	1 NFT
Corpus geniculatum mediale	Normal aspect, no dystrophic neurons	0 NFT
Colliculus superior	Cell rich, no atrophy, only a few dystrophic neurons	0 NFT, 1 dendrite
Oculomotor ncl	Normal aspect	4 NFT's
Trochlear ncl	Normal aspect	No tau pathology
Ventral tegmental area	Normal aspect	No tau pathology
Pontine nuclei	Cell rich, normal aspect (3 sections)	No tau pathology
Raphe pontis nuclei	1 dystrophic neuron	0 NFT, a few dendrites
Locus coeruleus	Normal aspect, no Lewy bodies (3 sections)	1 NFT, a few dendrites
Medial pontine tegmentum	Normal aspect	1 NFT
Abducens ncl	1 dystrophic neuron	No tau pathology
Medial parabrachial ncl	Normal aspect	No tau pathology
Motor trigeminal ncl	Normal aspect	No tau pathology
Facial ncl	Normal aspect	No tau pathology
Hypoglossal ncl	Normal aspect	No tau pathology
Dorsal vagal ncl	Normal aspect	1 NFT
Vestibular ncl	A few dystrophic neurons	No tau pathology
Spinal trigeminal ncl	A few dystrophic neurons	No tau pathology

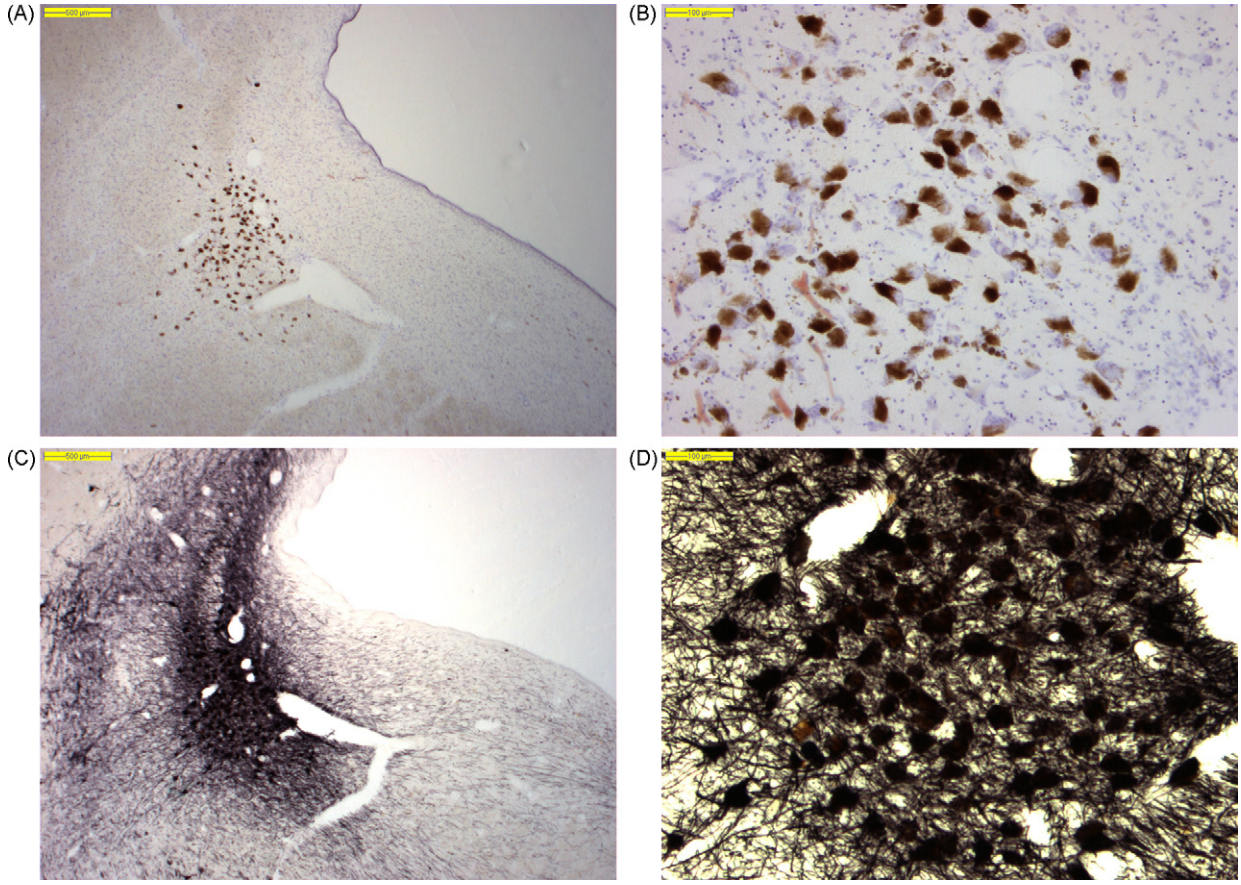

Fig. 2. (A) A micrograph of a 50 μm thick slice through the pons after Nissl staining, containing the pigmented neurons of the locus coeruleus, which are shown in more detail in (B). (C) and (D) show the next slice, which was immunohistochemically stained for tyrosine-hydroxylase (TH). From serial Nissl and TH sections cells were counted.

4. Discussion

At birth the woman weighed only 1600 g, which at that time meant a very low chance of survival. Yet she reached the age of 115. One of the most intriguing findings was that her body showed no significant atherosclerosis, and her brain no vascular pathology, only a slight amount of tau-pathology. Knopman et al. (2003) found in 87% of cognitively normal elderly (aged between 74 and 95 years) a so-called Braak-stage lower than 4. However, in 95% of these brains moderate plaques and small, old infarcts were common, while in the brain of this woman no plaques or infarcts were found. It is important to realize that Braak-stage 2, as was found in her brain, does not reflect pathological symptomatology, because studies across the age spectrum suggest that initial clinical symptoms of Alzheimer-disease neuropathology corresponds with at least Braak-stage 4 while stages 5 and 6 correspond with fully developed disease. Moreover, Alzheimer-disease neuropathology precedes clinical symptomatology by several years or even decades (Braak and Braak, 1997).

The number of locus coeruleus (LC) neurons found in this brain corresponds with the number found in people with healthy brains aged 60–82, while in individuals aged 103–104 only about 9500 cells were found (Manaye et al., 1995). According to Vijayashankar and Brody (1979) 16,500 LC cells corresponds with the number found in healthy persons under 60 years old. Not only the neuropathological results, but also the two neuropsychological assessments indicate that her brain was normal for individuals aged 75 years.

Our finding that she died from cancer (as did her father and two brothers) and not from any brain disease is consistent with the idea that centenarians (people that live longer than 100 years) do not die from "old age" but from a specific disease (Berzlanovich et al., 2005). The fact that her mother died at the age of 100 years, her grandparents from mother's side became 80 and 85 years old and that her two brothers and sister became 72, 82 and 80, respectively, suggest that genetic components may also play a role. It is clear that, if she had not died from cancer, she could have lived for several more years.

As we think that this very special case report is also interesting for other neuroscientists, we would like to emphasize that we are willing to share brain tissue samples. Either formalin-fixed frozen tissue or formalin-fixed paraf-

fin embedded tissue will be made available for anyone who is willing to collaborate with us. Furthermore, from several other organs snap frozen tissue is also available.

Conflict of interest

None.

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