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THE EFFECT OF AGE AND GENDER ON THE VOLUME AND SIZE DISTRIBUTION OF NEOCORTICAL NEURONS

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Abstract—Since the turn of the last century, the average life expectancy has risen considerably. Lengthening of life span has little merit if the quality of life is not preserved and in the elderly the decline in memory and cognitive abilities is of great concern. We applied a stereological technique, the planar rotator method, in an optical vertical design to get an estimation of the three-dimensional volume of the neocortical nuclei and perikaryon volume in neurons from brain neocortex and the four cortical lobes in 39 normal human subjects ranging from 18 to 93 years old. Although there was a trend with *p* values of 0.07, the mean global neocortical perikaryon volume was not significantly larger in men compared with women and the mean neuronal nuclear volume was not significantly different in the two sexes. Nonetheless, we found gender differences in both frontal and temporal cortices in the perikaryon volume, but not in the nucleus volume. Earlier findings of a higher neocortical neuron number in men compared with women was repeated in this study and, not unexpectedly, the sum of all neuronal perikaryon volume in neocortex was significantly higher in men than women, primarily as a result of a higher neocortical neuron number. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: aging, cell size, sex differences, human brain, neurostereology.

The life expectancy in the population of the Western world increased during the last century, which led to a larger elderly population that suffers from age-related disabilities, such as decline in memory and cognitive impairments. Aging of the human brain and gender differences have always been subjects of general interest. A decrease in the volume of the brain and gyral atrophy are common findings in the postmortem brain of aged individuals, and a loss of neurons in various regions is often reported, although it requires more time-consuming investigations (Esiri et al., 1997). Also, gender affects the human brain and stereological studies provided cell numbers and changes in fiber length in line with the vast literature on the effect of age and gender. A stereological study by Pakkenberg and Gundersen (1997) on 94 normal subjects ranging from 18 to 93 years reported a 9.8% global neocortical neuron loss recorded with age, demonstrating no regional differences, and 16% more neocortical neurons in men than women. Reductions by 45% from 20 to 80 years old in the total length of subcortical white fibers in the aging brain was also reported with gender differences in white fiber length of 17%, favoring men (Marner et al., 2003).

A number of data exist for the estimation of cell size in the CNS, but modern stereological tools have only been available for a few decades. Hence, most data on cell volumes were obtained from two-dimensional area profiles giving obvious difficulties in interpretation of results due to the three-dimensional cell volumes. Stereological methods may provide more accurate estimates of neuronal number and cell volume without the methodological assumptions of conventional morphometric techniques (see, e.g., Gundersen, 1986; Gundersen et al., 1988).

The aim of this study was to identify the normal range of the volume of the cell nuclei and the cell perikarya of neocortical neurons in the human brain according to gender and age. We used a combination of the Cavalieri estimator of macroscopic volumes, the optical disector for cell counting, and the planar rotator in a vertical design for estimation of cell volume (Baddeley et al., 1986; Jensen and Gundersen, 1993). In brain disorders studied so far, including brains of subjects with Alzheimer's disease (AD), chronic alcoholic subjects, and patients with schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and acquired immune deficiency syndrome (AIDS), only those subjects with AIDS had a significant reduction in global neocortical neuron number (Jensen and Pakkenberg, 1993; Oster et al., 1995; Regeur et al., 1994; Gredal et al., 2000; Pedersen et al., 2005; Toft et al., 2005). However, before nerve cells die, they are likely to show changes in volume. It can therefore be argued that cell body volume is an earlier and more sensitive parameter to changes in structure and function than cell numbers. Thirty-nine brains of subjects free of any disease known to influence neurological or psychiatric function and with an age range from 18 to 93 years were included in the study.

EXPERIMENTAL PROCEDURES

From a larger Danish brain bank formed for the purpose of stereological research and used for a large number of previous studies (see, e.g., Regeur and Pakkenberg, 1989; Pelvig et al., 2003; Andersen et al., 2003; Samuelsen et al., 2003), 40 brains from healthy Danes were selected for this study. All brains were collected in accordance with Danish laws governing the use of postmortem tissue in research. One specimen was excluded because of histological quality that was too poor to provide volume

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Abbreviations: AD, Alzheimer's disease; AIDS, acquired immune deficiency syndrome; ALS, amyotrophic lateral sclerosis; IUR, isotropic, uniform and random; 2D, two-dimensional.

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estimations. The material thus comprised 39 brains, 19 brains from women, 18–93 years old (average age, 63.9 years) and 20 men 19–87 years old (average age, 51.5 years). The average fixation time was 29 months (range 6–48 months) with no difference between males and females. None of the subjects had been assessed psychologically, but information about their prehospital life was obtained from either close relatives or their general practitioner. In Denmark people tend to live in the same neighborhood most of their lives, so the local practitioners and hospital departments know their patients well. The hospital files of the donors, the autopsy report, and some files from local practitioners were carefully studied to exclude individuals with diseases that might affect the CNS, such as cerebrovascular diseases, metastatic cancer, diabetes, hypertension, or abuse of alcohol or drugs. The age, sex, cause of death, postmortem interval, and body height and body weight are given in Table 1.

Sampling

All brains were fixed in 0.1 M sodium phosphate-buffered formaldehyde, (pH 7.2, 4% paraformaldehyde (PFA)) for at least 5 months before the meninges were removed and the cerebellum and brainstem were detached at the level of the third cranial nerve. Right or left hemispheres were chosen systematically with a random start between the first (right or left) hemisphere. The frontal, temporal, parietal, and occipital regions were delineated on the pial surface in different colors for later identification. The hemispheres were embedded in 6% agar and sliced coronally at

Table 1. Donor data

Gender	Age (y)	Cause of death	PMI (h)	Body height (cm)	Body weight (kg)
Female					
	18	Homicide (stabbing)	48	177	68
	30	Bronchopneumonia	72	157	56
	32	Embolia pulmonis	19	180	88
	39	Rupture of vena cava	24	163	66
	47	Morbus cordis	72	162	72
	53	Acute myocardial infarction	12	162	74
	57	Morbus cordis	12	163	79
	61	Acute myocardial infarction	48	167	81
	62	Acute myocardial infarction	96	158	60
	64	Acute myocardial infarction	20	154	50
	72	Embolia pulmonis	24	183	81
	72	Acute myocardial infarction	24	152	53
	80	Incompensatio cordis	12	162	47
	81	Acute myocardial infarction	54	157	51
	85	Acute myocardial infarction	31	159	39
	89	Acute myocardial infarction	28	153	55
	90	Pneumonia	13	167	52
	90	Peritonitis	12	165	60
	93	Embolia	12	156	66
Average	63.9		33		
Min	93				
Max	18				
Male	19	Fire, carbon dioxide poisoning	24	175	68
	19	Rupture cordis	48	178	67
	22	Suffocation (aspiration)	60	182	72
	28	Murder	12	180	76
	37	Acute myocardial infarction	40	182	76
	39	Embolia cordis	72	183	80
	40	Acute myocardial infarction	60	179	85
	44	Embolia pulmonis	24	185	88
	44	Embolia pulmonis	18	181	93
	48	Acute myocardial infarction	24	186	110
	54	Acute myocardial infarction	96	174	86
	55	Acute myocardial infarction	72	174	77
	57	Acute myocardial infarction	24	180	92
	60	Acute myocardial infarction	24	175	73
	67	Acute myocardial infarction	37	162	70
	70	Acute myocardial infarction	48	158	56
	74	Acute myocardial infarction	23	167	62
	81	Ulcus ventriculi	12	167	62
	84	Acute myocardial infarction	24	155	85
	87	Acute myocardial infarction	48	160	56
Average	51.4		39		
Min	87				
Max	19				

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