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ORIGINAL ARTICLE

Is There a Correlation Between the Number of Brain Cells and IQ?

Nicharatch Songthawornpong[1,†], Thomas W. Teasdale[2,†], Mikkel V. Olesen[1] and Bente Pakkenberg[1,3]

[1]Research Laboratory for Stereology and Neuroscience, Department of Neurology, Bispebjerg-Frederiksberg Hospital, DK-2400 Copenhagen, Denmark, [2]Department of Psychology, Faculty of Social Sciences, University of Copenhagen, DK-1353 Copenhagen, Denmark and [3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark

Address correspondence to Bente Pakkenberg, Research Laboratory for Stereology and Neuroscience, Bispebjerg-Frederiksberg Hospital, Nielsine Nielsens Vej 6B, Building 11B, 2. Floor, 2400 Copenhagen, Denmark. Email: bente.pakkenberg@regionh.dk.
[†]Nicharatch Songthawornpong and Thomas W. Teasdale are joint first authors

Abstract

Our access to a unique material of postmortem brains obtained from decades of data collection enabled a stereological analysis of the neuron numbers and correlation of results with individual premorbid intelligence quotient (IQ) data. In our sample of 50 brains from men, we find that IQ does not correlate with the number of brain cells in the human neocortex and was only weakly correlated to brain weight. Our stereological examination extended to measures of several other parameters that might be of relevance to intelligence, including numbers of cerebral glial cells (astrocytes, oligodendrocytes, and microglia) and the volume of key areas in the gray and white matter and of the cerebral ventricles, also showing near-zero nonsignificant correlations to IQ.

Key words: Børge Priens Prøve (BPP), cell numbers, human brain, intelligence quotient, stereology

Introduction

The definition and measurement of human intelligence has been one of the most significant developments in the history of psychological science, with major theoretical and practical implications. Intelligence, defined as a general cognitive ability, is often measured as an intelligence quotient (IQ). This index is well established and highly reproducible; it remains largely stable throughout adult life and is relatively independent of the method used to measure it (Mackintosh 2011). Scores in two of the most internationally used intelligence tests, the Wechsler's Adult Intelligence Scale (WAIS) and Raven's Progressive Matrices (RPM), typically have a correlation coefficient of ~0.7 or higher, despite being assessed in almost entirely different settings (McLeod and Rubin 1962). From childhood onwards, IQ has a close link to academic performance and the individual's future professional attainment, whereas negative social factors such as drug and alcohol abuse, and criminality in general are associated with a relatively low IQ (Mackintosh 2011). There is strong evidence that differences in intelligence are not only functional, but also have an organic basis. The presence of a well-established and substantial genetic contribution to intelligence (Deary et al. 2012, Bouchard 2014) has led to numerous imaging studies correlating intelligence and the anatomy of the brain. Accordingly, previous volumetric studies have reported a specific link between intelligence and the total volume of the brain's gray matter, while others have reported correlations with the volume of the cerebral cortex (Luders et al. 2009) and other areas of the brain (Ganjavi et al. 2011).

Magnetic resonance (MR) imaging enables the acquisition of brain volumetric data in individuals with present documentation of IQ and other traits. To our knowledge, only one in vitro study has tested for such correlations in a comparatively

large number of individuals (Witelson et al. 2006). That study compared postmortem brain volumes with premorbid IQ test scores (WAIS) obtained from 100 non-neurological patients, reporting a small positive correlation between IQ and brain volume. Gender, handedness, and specific scores in WAIS subtests all modulated this finding. However, Witelson et al. (2006) considered only gross brain weight and did not examine the microscopic details of the brain. Thus, it remains unknown whether intelligence correlates with the number of brain cells.

It has not previously been possible to test for correlations of IQ with numbers of specific cell populations because this requires the application of stereology in brains from individuals for whom there is documentation of premorbid IQ. Stereology is a discipline that is based on mathematically and statistically proven methods, that when applied properly, lead to unbiased results. The present material is, to our knowledge, unique, and is the product of a decades long brain collection program. We aimed to test the hypothesis whether intelligence correlates with the number of neurons in the cerebral cortex and its subregions. In addition, we measured several other parameters that might be of relevance to intelligence, including cerebral glial cell (astrocytes, oligodendrocytes, and microglia) numbers and the volumes of key areas in the gray and white matter, and of the cerebral ventricles.

Materials and Methods

Patients

Fifty-two brains from individuals for whom there was documentation of premorbid IQ, were available for the study. Of these, we had to exclude two brains for technical reasons, leaving us with brains from 50 Danish males aged 20–52 years at death, which was due to various non-neurological diseases (Table 1).

The brains had been collected between 1985 and 1991, at a time where there were no donation programs in Denmark and where the vast majority of people died at the hospital. The collection and treatment of brains were all conducted in strict accordance with Danish laws regarding autopsied human tissue at that time, thus providing a unique consecutive collection of brains of Danish men. The Danish Data Protection Agency (j. nr: 2012-58-0004) has approved the Brain Bank. Some of the studied subjects have been used in previous studies from our laboratory. We have reused tissue blocks and sections from 24 of the brains and obtained 26 new brains solely for this project. All the cell counts were performed de novo in the 50 brains and by the same stereologist. We included four cases with a history of alcohol dependence and six cancer patients. This is justified by our previous work showing that chronic alcoholics do not lose neocortical neurons (Jensen and Pakkenberg 1993), and by the absence of cases dying with coma, cachexia, or otherwise any prolonged agonal interval. Following data acquisition, it transpired that neocortical cell numbers of the four cases with alcohol dependence did not deviate from those of remainder of the sample ($P = 0.13$). Likewise, neocortical numbers in the cancer subgroup did not differ from that in the remainder of the sample ($P = 0.36$). None of the included cases had met exclusion criteria for drug abuse, psychiatric disturbances, diabetes, hypertension, or dementia.

Tissue Preparation

All the brains were stored in fixative (10% neutral buffered formalin, pH = 7.2) for at least 5 months before being studied. Right or left hemisphere was chosen systematically at random. The frontal-, temporal-, parietal-, and occipital lobes were delineated and painted with different colors of water-proof ink to distinguish the brain regions from each other (Pakkenberg and Gundersen 1997). The sampled hemispheres were embedded in agar before being cut into 4.25-mm thick slabs with a random starting point within a 4.25 mm interval. All the slabs were then photographed for estimating the total volumes, surface areas, and cortical thickness using point counting, test-lines, and the Cavalieri estimator (Gundersen and Jensen 1987). Then, 2-mm thick columns (i.e., rods) were sampled systematically at random from every third slab. About 8–12 rods were subsampled from each cortical lobe before being dehydrated in a gradient ethanol series and randomly rotated around the vertical axis (Fig. 1 and corresponding text in Pakkenberg and Gundersen 1997). The seemingly low number of tissue samples required for sampling in one brain is calculated from the principles of systematic, uniform, and random sampling, which allows the investigator to obtain any desired precision. The rods were embedded in Historesin (2-hydroxyethyl methacrylate, Kulzer, Germany) followed by cutting of a central 40-µm thick section that was stained using a modified Giemsa solution, and then used for cell counting. During the preparation of the rods intended for cell counting, extra rods were collected to measure shrinkage before and after processing. No net shrinkage was detected.

Estimation of Cell Numbers

To estimate the total cell numbers (Gundersen 1986), we used optical disectors, which are 3D probes consisting of an unbiased counting frame (Gundersen 1977) that can be moved in the z-direction down through the tissue section. We used an Olympus BX50 microscope equipped with a motorized x–y stage (Märzhäuser, Germany) and a microcator for z-analysis (Heidenhain, Germany). The tissue images were captured with a high-resolution color video camera (Basler, Germany), and projected onto a computer screen, where optical disectors were applied using NewCAST software (Visiopharm, Hørsholm, Denmark). In the present study, the area of the unbiased counting frames was set to 5000 μm^2 in the frontal-, parietal-, and temporal lobes, and 2500 μm^2 in the occipital lobe. Based on z-distribution analysis, the average section thickness was 40 µm, resulting in a disector height of 15 µm, a 5-µm guard zone at the top of the sections and a 20-µm guard zone of at the bottom of the section. The step-length between sampling sites was set to 1000 µm.

The different cell types were identified by accepted morphological criteria, with neurons having a large nucleus, single dark stained nucleolus and a visible cytoplasm. Oligodendrocytes were small and rounded, with no visible cytoplasm, astrocytes were larger than oligodendrocytes and with a pale nucleus and a granulated appearance, and microglia were small, comma-shaped cells (Garcia-Cabezas et al. 2016). Since the cell counts were performed using Giemsa-stained sections, our results are based on cell morphology alone. However, astroglia-, oligodendroglia-, microglia-, and neuron-specific immunohistochemistry has ongoingly corroborated our cell-identification criteria (Salvesen et al. 2017). The cell counts were performed using a ×60 oil-immersion objective (numerical aperture = 1.42, Olympus, Denmark) at a final on-screen magnification of ×1380.

Table 1 Demographic and autopsy-related data

Age at death	Body height (cm)	Body weight (kg)	Occupation	Cause of death	Brain weight (g)	IQ
20	178	67	—	Ruptured heart	1500	94
21	185	—	Factory worker	Puncture of the heart	1400	89
21	183	77	Unemployed	Acute myocardial infarction	1485	95
28	180	76	Unemployed	Knife wound (homicide)	1400	90
33	176	—	Operator	Cancer of the rectum	1570	107
34	181	79	Special worker	Bleeding (homicide)	1230	83
35	176	86	—	Acute myocardial infarction	1390	81
36	178	86	School teacher	Sepsis	1550	120
37	182	76	—	Acute myocardial infarction	1620	96
37	187	76	Innkeeper	Drowning	1446	73
38	180	96	Navigator	Acute myocardial infarction	1390	110
39	176	55	Electrician	Cardiomyopathy	1558	96
39	183	80	Fire inspector	Acute myocardial infarction	1550	109
39	179	85	Entrepreneur	Liver failure	1460	97
39	181	72	Laborer	Lung cancer	1210	108
39	187	96	—	Acute myocardial infarction	—	91
39	177	—	Engineer	Acute myocardial infarction	1860	113
40	179	85	Refinery worker	Acute myocardial infarction	1620	92
40	167	75	Caretaker	Acute myocardial infarction	1710	80
40	173	76	Brewer	Acute myocardial infarction	—	115
41	174	81	—	Cardiomyopathy	1432	106
41	186	79	—	Acute pancreatitis	1600	92
41	173	78	Welder	Terminal uremia	1240	107
41	190	87	Insurance agent	Lung cancer	1340	96
42	186	107	—	Aorta aneurysm	1500	116
42	167	61	Fisherman	Lung cancer	1460	78
43	170	80	—	Acute myocardial infarction	1150	82
43	176	89	Laborer	Acute myocardial infarction	1680	72
43	175	82	Haulier, plumber	Acute myocardial infarction	1560	89
43	172	89	Electrician	Acute myocardial infarction	1350	96
44	181	93	—	Pulmonary embolism	1610	93
44	172	81	Early retirement	Drowning	1500	86
44	179	89	Medical doctor	Acute myocardial infarction	1570	127
44	185	88	Chimney sweeper	Pulmonary embolism	—	99
45	186	82	Operator	Liver failure	1538	75
44	—	—	—	Acute myocardial infarction	1420	125
45	175	68	Operator	Acute lung edema	1350	106
46	186	66	Fitter	Pulmonary heart disease	1460	96
46	170	79	Baker	Hypernephroma	1520	104
46	174	—	Mechanic	Hypernephroma	1400	79
46	174	67	Disability pension	Liver failure	1500	107
47	176	81	Slaughterhouse worker	Acute myocardial infarction	1270	79
47	174	78	Concrete worker	Acute myocardial infarction	1630	88
47	172	88	Locksmith	Bleeding stomach ulcer	1519	94
47	180	77	Driver	Acute myocardial infarction	1579	95
48	176	46	—	Lung edema	1340	86
49	172	78	Laborer	Acute myocardial infarction	1400	62
49	175	74	Early retirement	Suicide with medicine[a]	1360	102
50	182	78	Carpenter	Aorta aneurysm	1760	109
52	171	77	Farmer, CEO	Acute myocardial infarction	1340	106
Mean (range)	174 [167–190]	71 [46–107]			1475 [1150–1860]	96 [62–127]

Note: [a]Died without any previously known diseases.

A uniform distribution of the cells within the disector height was confirmed by analyzing the z-distribution of particles.

To obtain the numerical density (N_V) of each cell type in one hemisphere (unilaterally), we used the following equation (Gundersen and Jensen 1987): $N_V = \sum Q^- / (V_{dis} \times \sum P)$, where $\sum Q^-$ is the total number of cells counted, V_{dis} is the volume of the disector, and $\sum P$ is the total number of disectors sampled in the region of interest. Then, the total number of cells is estimated by multiplying N_V with the Cavalieri volume ($V_{ref} = T \times (a/p) \times \sum P$, where T is the thickness of the slab, a/p is the area per point on the counting grid, and P_i is the number of points hitting the tissue within the region of interest). Finally, the total number of

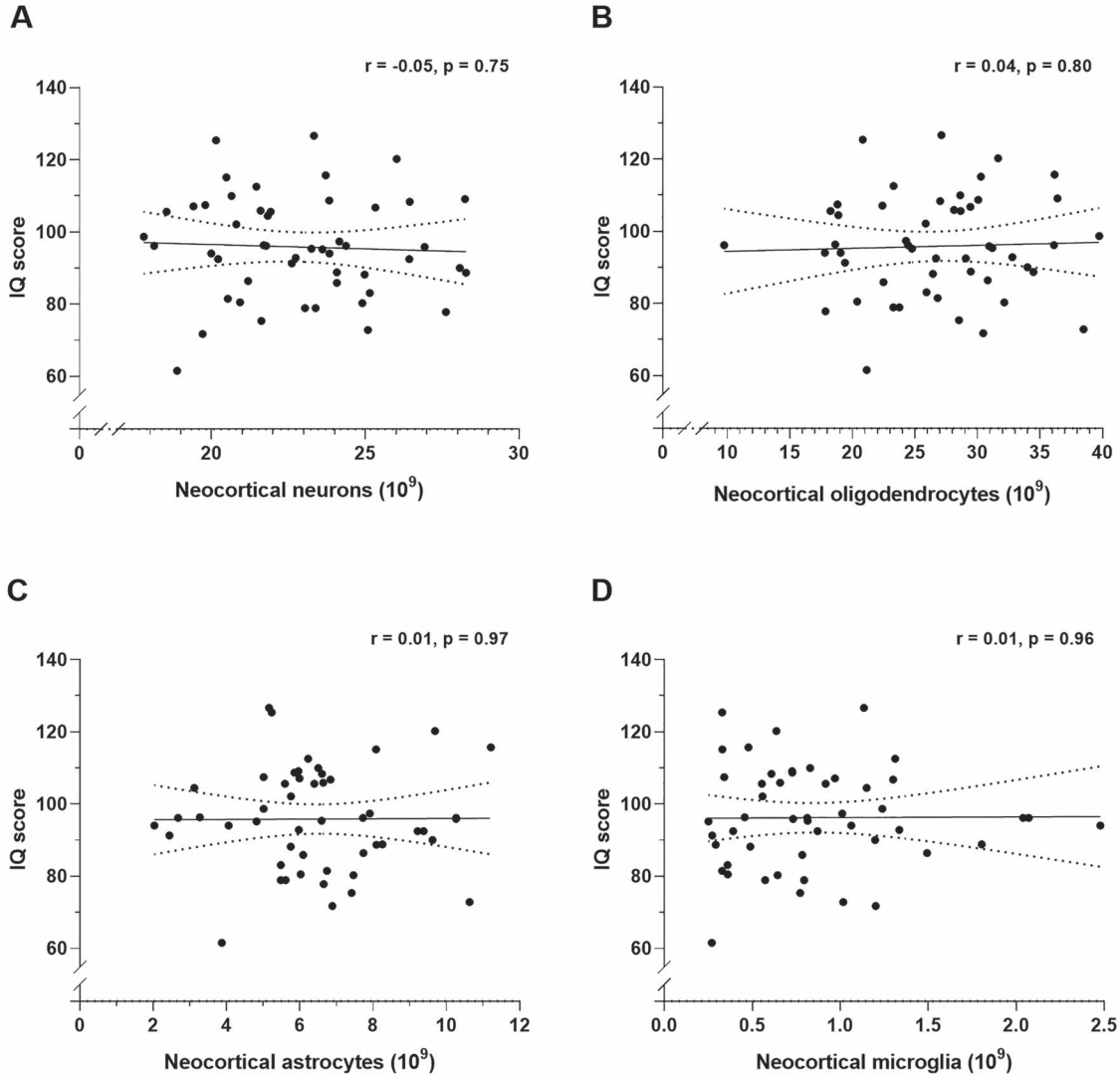

Figure 1. Pearson's correlation coefficients (*r*) between IQ score and estimates of total number of neocortical neurons (*A*, •), oligodendrocytes (*B*, •), astrocytes (*C*, •), and microglia (*D*, •). The correlations are shown with 95% confidence intervals (dotted lines).

Table 2 Power and confidence limits

Power			
r	*n*	Delta	Alpha
0.4	50	2.8	80%

Confidence limits		Neocortex							WM	CG
		Neurons	Astro	Oligo	Micro	Volume	Surface	Thickness	Volume	Volume
Pearson correlation IQ with		−0.05	0.01	0.04	0.01	−0.04	−0.12	0.11	−0.08	−0.001
Bootstrap, 95%	Lower	−0.33	−0.27	−0.23	−0.34	−0.32	−0.37	−0.17	−0.39	−0.25
confidence interval	Upper	0.24	0.27	0.28	0.17	0.22	0.15	0.38	0.22	0.28

each cell type was estimated by multiplying by two, to obtain bilateral numbers. These estimated results can have varying degrees of precision as determined by the investigator (indicated by the coefficient of error (CE)). In general, "optimal" precision is achieved when the CE value is less than half of the observed biological variance (CV), as $OCV^2 = ICV^2 + CE^2$, where OCV is the observed CV and ICV is the inherent CV (Boyce et al. 2010). According to this formula, we are able to adjust the CE to suit the CV by adjusting the amount of sampling. Since the biological variance of the total number of neurons between examined

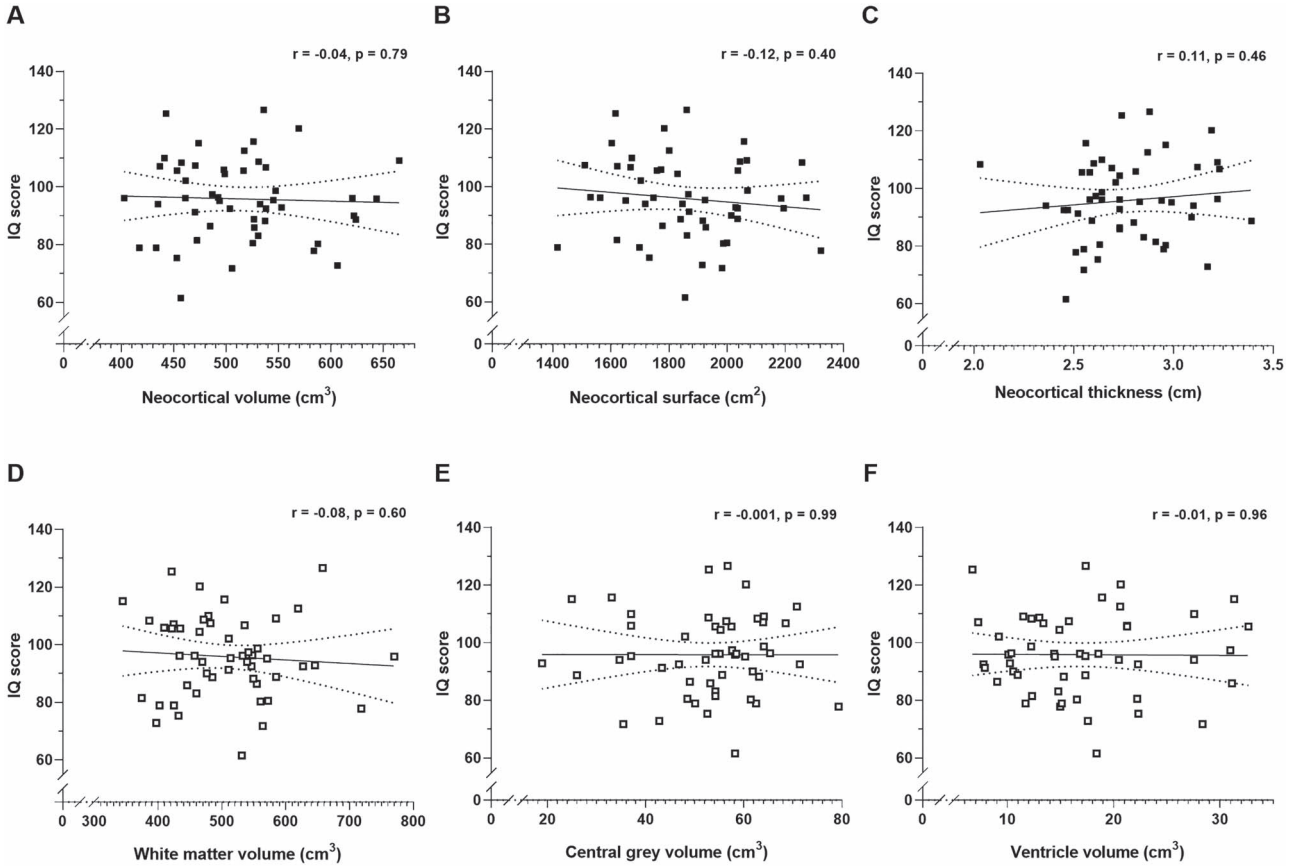

Figure 2. Pearson's correlation coefficients (*r*) between IQ score and estimates of total neocortical volume (*A*, ■), surface area (*B*, ■), and mean thickness (*C*, ■). Also shown are the correlations between IQ score and the volume of white matter, (*D*, □), central gray (*E*, □), and cerebral ventricles (*F*, □). The correlations are shown with 95% confidence intervals (dotted lines).

brains in this study was ~12%, we aimed at a precision of about half the biological variance (in this study ~4%).

IQ Scores

The IQ scores for the 50 men, who were 18–20 years of age at examination, were derived from an intelligence test used for evaluating potential recruits into the armed forces, the Børge Priens Prøve (BPP), which is a test correlating very highly with scores from the internationally used WAIS and Raven's IQ tests (Mortensen et al. 1989, Teasdale 2009). The BPP test, unchanged in content between 1957 and 2010, has been taken by ~90% of all Danish males at age 18+, and individual scores can be obtained retrospectively from computerized registers (Christensen et al. 2015). We retrieved the scores from the Danish Conscription Database, which has authorization from the Danish Data Registration Agency to release such data to be used in studies of intelligence and health (jr.nr: 2014-41-2911). The BPP has four subtests, totaling 78 items. The total score for the BPP has very satisfactory psychometric properties (Nielsen et al. 2019). The 50 men in the sample were born between 1937 and 1962, such that their BPP testing occurred during a period with markedly improved BPP performance (Teasdale and Owen 1987). Therefore, we transformed the raw BPP scores to IQs, adjusting for the generational difference (the so-called "Flynn effect," Trahan et al. 2014). This was achieved as follows. Using the Danish extensive population norms for the range of birth years, we computed IQ scores normed for the corresponding years, for example, the IQ for a man tested in 1970 was scaled from BPP score in relation to the mean and standard deviation for the ~25 000 men who had been tested in that year. Across our sample, the mean IQ was somewhat lower than the population average, but with very close to the expected variation (mean = 96, SD = 14), and therefore adequately represents the general population. Although there is little variation in the age at which IQ was measured, the ages at death ranged between 20 and 52 years. However, IQ varies little across the age range (Mackintosh 2011) and, indeed, the correlation coefficient for IQ as a function of age of death in our sample did not indicate any relationship ($r = 0.01$, data not shown).

Statistics

With $n = 50$, we had a power of 80% to detect a correlation between IQ and total neocortical neuron numbers of 0.34. Correlations were analyzed using Pearson's Product Moment formula and 95% confidence limits for these were calculated using Bootstrap procedures. The statistical analyses were performed using SPSS (vers. 26) and the significance was set at $P < 0.05$ (two-tailed). Graphical presentation was completed using GraphPad Prism (vers. 8). As can be seen in Table 2, correlations do not deviate significantly from zero and the confidence limits deviate widely around that value.

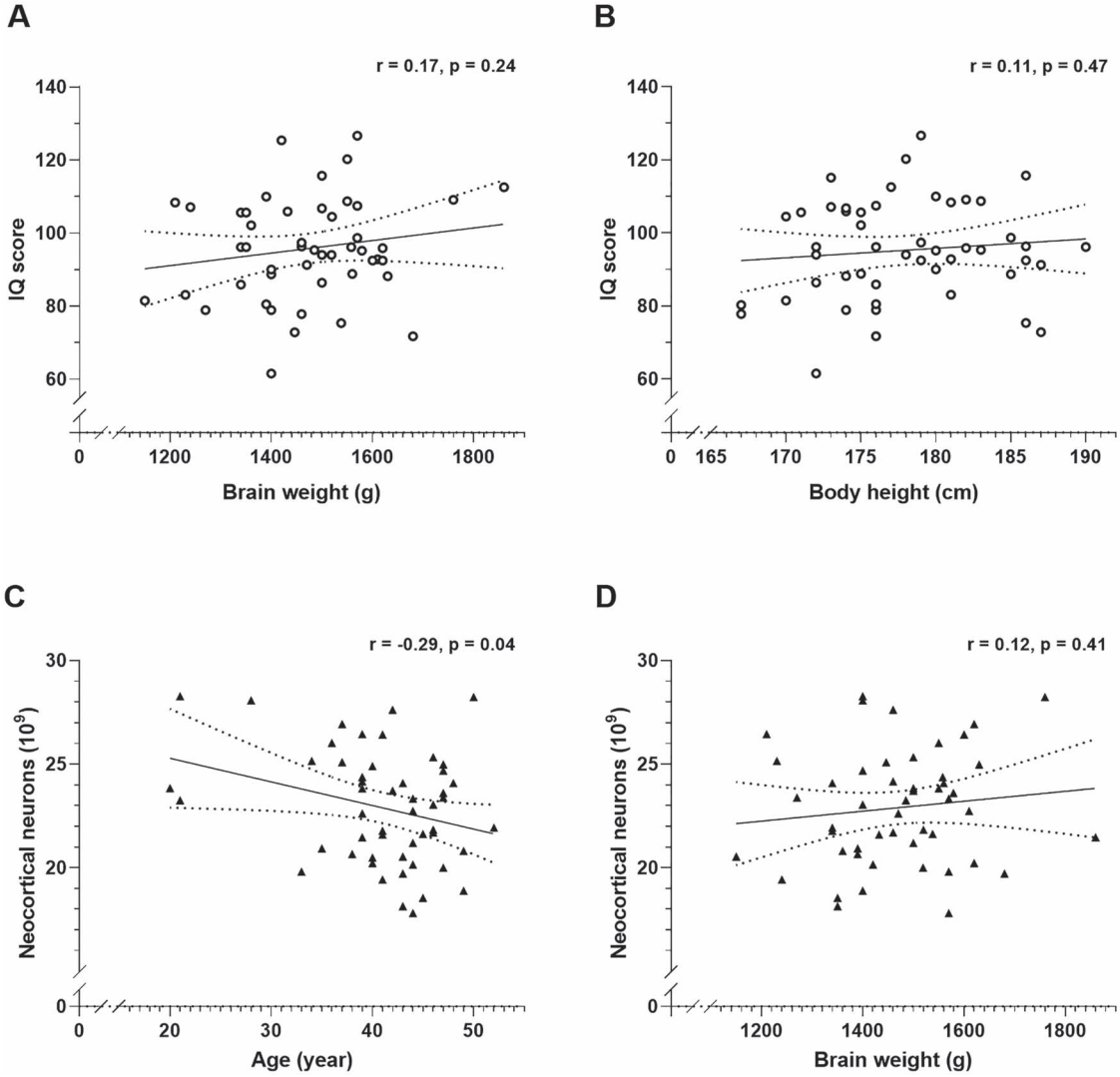

Figure 3. Pearson's correlation coefficients (*r*) between IQ score and brain weight (*A*, ○), and body height (*B*, ○) and correlations between total number of neocortical neurons and age (*C*, ▲), and brain weight (*D*, ▲). The correlations are shown with 95% confidence intervals (dotted lines).

Results

In our sample of 50 male brains, IQ scores did not correlate significantly with the total number of neurons (Fig. 1A), oligodendrocytes (Fig. 1B), astrocytes (Fig. 1C) or microglia (Fig. 1D) in the neocortex, nor with the cortical volume (Fig. 2A), surface area (Fig. 2B) and thickness (Fig. 2C). This also applied to estimates of the four separate lobes (frontal-, temporal-, parietal-, and occipital cortices; see Supplementary Material). Neither did IQ score correlate significantly with the volumes of white matter (Fig. 2D), central gray matter (Fig. 2E) or lateral ventricles (Fig. 2F), nor with the brain weight (Fig. 3A), or body height (Fig. 3B). All of these correlation coefficients were less than 0.2. Finally, the total number of neurons correlated negatively with age of death (Fig. 3C), but not brain weight (Fig. 3D).

Discussion

Large brains contain not only more neurons, but also more glia cells, more subcortical gray matter and a larger white matter fiber network compared with small brains (Marner et al. 2003), but none of these parameters correlated significantly with IQ in this study using a sample size of 50 male brains.

The repeated demonstration of a marked genetic contribution to intelligence (Bouchard 2014) implies some neural basis to variance in intelligence, but the present negative results in our sample of 50 male brains are not consistent with any important association with neocortical neuron numbers but rather could have relation to other factors such as network properties, synapse numbers or other structural components. Speculatively, the lack of significant correlations in this study might help to explain why the rather large difference in neocortical neuron number between men and women (16% higher in men, Pakkenberg and Gundersen 1997) does not match with the minor gender difference in IQ (Halpern and LaMay 2000) and that highly demented female Alzheimer's disease patients have normal neocortical neuron numbers (Regeur et al. 1994, Pelvig et al. 2003). One limitation of the present study is the small sample size, and our negative results must be interpreted with caution. Further, cell quantification was performed using

Giemsa-stained sections, and our results are therefore based on cell morphology alone. However, neuron-, oligodendroglia-, astroglia-, and microglia-specific immunohistochemistry verified our cell identification criteria.

As stated above, various reports correlating IQ-scores to estimates of brain size such as brain weight, head circumference, computed tomography- (CT) and MR imaging (MRI)-based brain volume estimates, have shown results with correlations ranging from 0 to 0.6 (Gignac and Bates 2017). The apparent link between brain volumes and IQ-scores may relate to factors such as cell density and/or neuronal circuit complexity, myelin thickness and dendritic arborization (Jung and Haier 2007). However, the great preponderance of studies on this topic is based on CT and MR imaging, which is uninformative about cell populations. In contrast to many IQ studies, our stereological data did not find that IQ correlates with macroscopic (brain weight, volumes, cortical thickness, and surface area) estimates. However, while MRI-based volumetric quantification offers high-resolution brain images of living participants, the results from CT or MRI studies cannot always be directly compared with results from physical sections. For example, Furlong et al. (2013) made a direct comparison between postmortem 3 T MRI and stereology on physical tissue sections from 16 cerebral hemispheres to estimate the volume of the cortex and subcortex, area of the pial surface and gray–white matter boundary, and thickness of the cerebral cortex. The results showed poor agreement between MRI and stereology, especially for pial surface (MRI = 1165 cm^2, stereology = 2134 cm^2, $P < 0.05$), thickness of the cerebral cortex (MRI = 3.7 mm, stereology = 2.3 mm, $P < 0.001$) as well as volume of the cerebral cortex (MRI = 530 cm^3, stereology = 454 cm^3, $P < 0.001$) and subcortex (MRI = 432 cm^3, stereology = 520 cm^3, $P < 0.001$). However, the two methods gave very similar results for whole brain volume (MRI = 962 cm^3, stereology = 974 cm^3, $P = 0.5$). The authors concluded that the major cause for the differences was due to the resolution of the MR images which was not sufficient to always allow reliable delineation of the cerebral sulci. Further, it should be recognized that the present lack of significant correlation between IQ and brain volumes may reflect the number of brains available for this analysis, which consequently affects the statistical power. Thus, with a sample size of $n = 50$, an 80% probability of finding a two-tailed significance would only be obtained, if the correlation was 0.4. This is a value above most reported studies finding positive brain volume-IQ correlations.

Our results found only minor relationships between IQ and neuroanatomical measures obtained from stereological analysis of physical sections. It may be, however, that dynamic functional measures, such as position emission tomography (PET) or functional MRI, have greater promise as correlates of intelligence. These methods measure neural metabolism and activity or functional connectivity between brain regions, which maybe therefore have a stronger functional correlation to intelligence as a property of living brains. For example, one PET study has examined the regional glucose metabolic rate in a small group of participants performing the Raven's Advanced Progressive Matrices (RAPM) (Jung and Haier 2007). That study showed an inverse correlation between high RAPM-scores and low regional glucose metabolic rate, which suggest the occurrence of increased "neuronal efficacy" in high-performing subjects. However, follow-up studies have produced conflicting results showing both increased and decreased brain metabolism in subjects with high RAPM-scores (Neubauer and Fink 2009, Basten et al. 2015).

In summary, this is the first study to estimate and correlate the total number of neocortical cells with IQ. In our unique collection of 50 consecutive collected male brains, we found no correlation between cell numbers and IQ. We speculate that this lack of correlation could be due to other factors being more important for IQ such as the neuronal circuit complexity, synapse numbers, or dendritic arborization.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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