



Multi-element Analysis of Brain Regions from South African Cadavers

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Abstract

Trace elements are vital for a variety of functions in the brain. However, an imbalance can result in oxidative stress. It is important to ascertain the normal levels in different brain regions, as such information is still lacking. Therefore, this study aimed to provide baseline trace element concentrations from a South African population, as well as determine trace element differences between sex and brain regions. Samples from the caudate nucleus, putamen, globus pallidus and hippocampus were analysed using inductively coupled plasma mass spectrometry. Aluminium, antimony, arsenic, barium, boron, cadmium, calcium, chromium, cobalt, copper, iron, lead, magnesium, manganese, mercury, molybdenum, nickel, phosphorus, potassium, selenium, silicon, sodium, strontium, vanadium and zinc were assessed. A multiple median regression model was used to determine differences between sex and regions. Twenty-nine male and 13 female cadavers from a Western Cape, South African population were included (mean age 35 years, range 19 to 45). Trace element levels were comparable to those of other populations, although magnesium was considerably lower. While there were no sex differences, significant anatomical regional differences existed; the caudate nucleus and hippocampus were the most similar, and the globus pallidus and hippocampus the most different. In conclusion, this is the first article to report the trace element concentrations of brain regions from a South African population. Low magnesium levels in the brain may be linked to a dietary deficiency, and migraines, depression and epilepsy have been linked to low magnesium levels. Future research should be directed to increase the dietary intake of magnesium.

Keywords Brain · Corpus striatum · Hippocampus · Inductively coupled plasma mass spectrometry · South Africa · Trace elements

Introduction

Trace elements are vital for a variety of functions in the brain, provided optimal concentrations are maintained. Several elements are involved in depression and anxiety, such as magnesium, zinc, copper, selenium and manganese [1, 2]. In some neurodegenerative diseases (Alzheimer's disease, Parkinson's

disease, Huntington's disease and multiple sclerosis), certain elements are increased or decreased in the affected brain regions [3, 4]. Alterations in trace element levels have also been observed with brain tumours [5]. Consequently, trace elements may be involved in these disorders [6]. An imbalance of certain trace elements can result in oxidative stress and damage, which can contribute to the aetiology of neurodegenerative diseases and brain tumours [7]. Thus, it is important to establish baselines for trace element levels in different regions of the brain. With this knowledge, the molecular biology of certain neurodegenerative diseases can be better understood.

To the authors' best knowledge, the trace element brain levels of the South African population have not been investigated. Different populations are exposed to different element quantities, depending on the levels in water, air, food and soil [8, 9]. Inadequate or excess trace element levels in the brain may predispose a population group to neurodegenerative diseases. Moreover, male and female trace element levels may be different due to hormonal differences [10], and it would be of interest to establish if males or females could be more prone to neurodegenerative disease. Regional differences in trace elements have been noted in the brain; however, baseline

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information is sparse regarding trace elements in certain regions. As trace element levels are related to function [11], and if certain areas are affected differently by trace element levels, this may assist with the aetiology of neurodegenerative diseases. Therefore, this study aimed to firstly, provide baseline trace element concentrations from a South African population group within the Western Cape region, secondly, to determine trace element differences between males and females, and lastly, to determine the brain regional trace element differences.

Methodology

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Health Research Ethics Committee, Stellenbosch University, S17/09/183) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the Legally Authorized Representative or from the next of kin.

Subject Specifics

Male and female cadavers were included from a South African population within the Western Cape, between the ages of 18 and 45. Individuals older than 45 were excluded to limit neurodegeneration due to age or dementia. Further exclusion criteria included trauma to the head, evidence of neurodegeneration (visible atrophy, increased ventricles and sulcal space) and presence of tumours since these factors may affect the trace element concentration. The caudate nucleus, putamen, globus pallidus and hippocampus were removed from the right hemisphere and stored in sterile tubes containing 10% buffered formalin. These regions were selected since studies have commonly investigated the trace element imbalances in these regions.

Sample Preparation

The methodology of Corrigan et al. [12] was used; however, brains were removed from formalin embalmed cadavers. Cadavers are routinely embalmed upon arrival to ensure longevity and reduced the transmission of infections. After formalin embalming, the brains were removed and cut in 1-cm horizontal sections. Between 0.2 and 1.0 g of tissue was sampled from the head of the caudate nucleus, putamen and globus pallidus at the level where the distinction between the globus pallidus and putamen becomes evident. The hippocampus was sampled at the next horizontal section.

Tissue was pre-digested for 15 min in Teflon beakers with an acid solution of 1.0 mL H₂O₂ (30%) and 6.0 mL HNO₃ (> 69%). Samples were heated in the CEM Microwave Accelerated Reaction System (MARS 5: 800 psi, 210 °C, ramp = 25 min, hold = 10 min). Afterwards, 1.0 mL content was placed in plastic tubes containing 9.0 mL HCL (0.5%).

Element Analyses

Analyses were performed at the Central Analytical Facility, Stellenbosch University, South Africa. Digested brain samples were analysed using inductively coupled plasma mass spectrometry (Agilent 7900 ICP-MS, Agilent Technologies, United States of America), and parameters are specified in Table 1. National Institute of Standards and Technology (NIST) traceable standards (calibration acceptance criteria: $R^2 > 0.9995$) were used for calibration and the United States Environmental Protection Agency (US EPA) guidelines were used for quality control (quality control standard: IV-28, Inorganic Ventures, United States of America). Table 2 indicates the quality control accuracy of each element. The following elements were assessed: aluminium, antimony, arsenic, barium, boron, cadmium, calcium, chromium, cobalt, copper, iron, lead, magnesium, manganese, mercury, molybdenum, nickel, phosphorus, potassium, selenium, silicon, sodium, strontium, vanadium and zinc. A formalin blank was included to exclude contamination.

Statistical Analysis

Descriptive statistics on trace element concentrations were done using median and interquartile ranges for each region. A multiple quantile (median) regression model was used to determine if there were significant differences in trace element concentrations between males and females, and between different brain regions, adjusting for the correlation of the measurements within the same participant. A *t* test was done to determine if there were significant differences in ages between males and females. Since multiple brain regions ($n = 4$) were compared the significance of brain region as a factor was assessed using a post hoc chi-square test and if significant, pairwise contrasts were investigated. A power analysis was completed to ensure an 80% power, and significance was determined at $p < 0.05$. Statistical analysis was performed using STATA (StataCorp, version 15.1).

Results and Discussion

Forty-two cadavers were included, 29 males (35.7 ± 6.5 , range 19 to 45) and 13 females (33.5 ± 7.2 , range 23 to 43). There were no significant differences between ages as determined by the *t* test. Most or all the values of aluminium, antimony,

Table 1 Parameters of Agilent 7900 ICP-MS

Parameter	Value	Unit
RF power	1600	W
Carrier gas (argon)	0.83	L min ⁻¹
Sample depth	10.00	Mm
Make-up gas	0.15	L min ⁻¹
He flow	5.00	mL min ⁻¹
H ₂ flow	6.00	mL min ⁻¹
Nebuliser	0.40	mL min ⁻¹ Micro mist
Element	Cell gas	Integration time (s)
⁷ Li, ⁹ Be, ¹¹ B	No gas	0.1
⁸⁸ Sr, ¹³⁷ Ba	He	0.1
⁷² Ge, ¹⁰³ Rh, ¹¹⁵ In, ¹¹⁸ Sn	He	0.2
²⁷ Al, ⁴⁵ Sc, ⁵¹ V, ⁵² Cr, ⁵⁵ Mn, ⁵⁶ Fe, ⁵⁹ Co, ⁶⁰ Ni, ⁶³ Cu, ⁶⁶ Zn, ⁸⁹ Y, ⁹⁵ Mo, ¹¹¹ Cd, ¹²¹ Sb, ²⁰¹ Hg, ²⁰⁸ Pb, ²⁰⁹ Bi	He	0.3
⁷⁵ As, ⁷⁷ Se	He	0.5

arsenic, boron, chromium, cobalt, lead, molybdenum, nickel, potassium, silicon and vanadium were below the detection limit and were excluded from further analysis. Thus, this study reports the concentrations of iron, zinc, copper, manganese, selenium, calcium, magnesium, phosphorus, sodium, strontium, barium, cadmium and mercury.

Population Differences

Trace elements levels in the brain have been studied on healthy or ageing populations from Austria [13], Belgium [14], Brazil [15, 16], Canada [17–19], Denmark [20, 21], Germany [22, 23], Hungary [24–28], India [4, 29], Japan [30], Netherlands [31], Portugal [7, 32, 33], the UK [12, 34, 35] and the USA [3, 36–43]. Table 3 summarises the concentrations of the elements observed in the present study and in

Table 2 Quality control accuracy of each element (%)

Element	Accuracy	Element	Accuracy
Aluminium	107.19%	Manganese	95.58%
Antimony	100.72%	Mercury	90.69%
Arsenic	100.12%	Molybdenum	100.50%
Barium	99.79%	Nickel	99.11%
Boron	103.54%	Phosphorus	102.50%
Cadmium	98.80%	Potassium	110.34%
Calcium	107.33%	Selenium	99.14%
Chromium	98.69%	Silicon	93.33%
Cobalt	99.01%	Sodium	104.72%
Copper	102.92%	Strontium	99.48%
Iron	101.83%	Vanadium	99.57%
Lead	100.62%	Zinc	104.86%
Magnesium	111.19%		

the literature. Table 4 summarises the methodology of the studies reported in Table 3.

Iron

Iron is vital for normal brain functioning, myelination, neurotransmitter synthesis and a cofactor for numerous enzymes [41]. Moreover, iron is a catalyst of reactive oxygen species (ROS), since iron transfers single electrons as it interchanges between reduced and oxidised states [31]. Iron accumulation results in ROS formation, membrane and DNA damage, as well as protein aggregation [22]. Low iron levels can result in poor myelination and cause mental deficits [44]. Our results (23.6 to 103.2 µg/g) were similar to reports from India [4, 29], USA [36, 39–41], the UK [12, 34], Canada [18], Brazil [15, 16] and Austria [13]. However, most other studies observed higher iron concentrations (239.0 to 1056 µg/g), such as Belgium [14], Canada [17, 19], Germany [22, 23], Hungary [24–26], Japan [30], Portugal [7], UK [19, 35] and USA [37, 38]. Sources high in dietary iron include high protein foods such as red meat, seafood, poultry, beans and lentils. These differences may be due to the socioeconomic status of the cadavers selected for the studies. Developing countries and low socioeconomic groups tend to consume significantly less protein (and iron) compared with the world average [45, 46], and iron deficiency is the most common nutritional deficiency [47]. Additionally, the protein consumed may be of a lesser quality [48].

Zinc

Zinc is a cofactor for over 200 enzymes, and important for normal brain functioning, neurotransmitter functioning, as well as axon bundle development [12, 31, 43]. A zinc deficiency can result in delayed growth, wound healing and

Table 3 Average concentrations of several elements in different brain regions of healthy individuals from different countries ($\mu\text{g/g}$)

	South Africa*	Austria	UK	Canada	USA	Germany	Portugal	Hungary	Other	
Iron	Caudate nucleus	47.1 \pm 18.4	106.0 \pm 26.0 [13]	99.6 \pm 6.6 [34]	651.0 \pm 44.0 [17]	93.1 [36] 535.0 \pm 132.3 [37] 714.8 \pm 39.1 [38] 85.8 \pm 24 [36]	323.2 \pm 115.0 [22] 830.0 \pm 159.3 [23]	599.0 \pm 271.0 [7]	640.0 \pm 100.0 [24] 653.0 \pm 174.0 [25]	Belgium: 520.0 \pm 180.0 [14] Japan: 525.0 \pm 154.0 [30]
	Putamen	65.5 \pm 28.6	159.3 \pm 36.7 [13]	119.8 \pm 11.6 [34]	75.0 \pm 10.0 [18]	136.0 [39] 586.0 \pm 192.9 [37] 608.7 \pm 67.0 [38]	578.8 \pm 167.6 [22] 878.0 \pm 173.9 [23]	739.0 \pm 390.0 [7]	760.0 \pm 40.0 [26] 840.0 \pm 100.0 [26] 910.0 \pm 190.0 [24]	Belgium: 610.0 \pm 240.0 [14] Japan: 683.0 \pm 176.0 [30]
	Globus pallidus	103.2 \pm 32.1	202.7 \pm 37.8 [13]	163.8 \pm 18.3 [34] 207.0 \pm 9.7 [34]	134.0 \pm 43.0 [18]	132.7 [36] 169.0 [39] 710.0 \pm 226.3 [37] 776.2 \pm 61.4 [38]	523.7 \pm 95.3 [22] 1056.0 \pm 273 [23]	855.0 \pm 295.0 [7]	830.0 \pm 300.0 [24]	Belgium: 820.0 \pm 200.0 [14] Japan: 729.0 \pm 243.0 [30]
	Hippocampus	23.6 \pm 11.5	–	49.8 \pm 7.8 [12] 427.7 [19]	456.4 [19]	42.1 \pm 1.9 [40] 43.8 [39] 52.0 \pm 13.7 [41] 156.4 \pm 16.8 [38] 216.0 \pm 53.1 [42] 219.0 \pm 36.9 [37]	238.0 \pm 60.1 [23]	239.0 \pm 54.0 [7]	240.0 \pm 20.0 [26]	India: 26.6 \pm 7.6 [4] India: 27.9 \pm 1.7 [29] Brazil: 199.7 \pm 37.6 [15] Brazil: 202.4 \pm 38.2 [16]
Zinc	Caudate nucleus	5.5 \pm 2.6	12.4 \pm 2.9 [13]	56.0 \pm 8.0 [35]	7.0 \pm 11.1 [17]	15.6 [39] 81.0 \pm 20.8 [37]	44.4 \pm 9.7 [22] 86.3 \pm 12.5 [23]	61.0 \pm 13.0 [32]	77.5 \pm 6.6 [25] 80.0 \pm 7.0 [24] 81.0 \pm 4.0 [25]	Japan: 112.0 \pm 69.0 [30]
	Putamen	6.8 \pm 25.7	12.0 \pm 2.5 [13]	62.3 \pm 5.8 [35]	–	75.0 \pm 12.9 [37]	50.7 \pm 8.5 [22]	62.0 \pm 11.0 [32]	78.1 \pm 4.0 [26] 90.0 \pm 13.0 [25] 91.0 \pm 20.0 [24] 91.7 \pm 10.0 [26]	Japan: 108.0 \pm 113.0 [30]
	Globus pallidus	8.4 \pm 22.8	12.7 \pm 2.5 [13]	–	–	12.0 [39] 69.0 \pm 15.7 [37] 15.2 \pm 0.5 [43] 15.2 \pm 4.6 [41] 15.8 \pm 0.6 [40]	34.2 \pm 6.4 [22] 52.5 \pm 10.5 [23] 96.3 \pm 14.9 [23]	45.0 \pm 11.0 [32]	67.0 \pm 5.0 [25] 68.0 \pm 5.0 [24] 86.0 \pm 5.0 [25]	Japan: 91.0 \pm 38.0 [30]
	Hippocampus	6.1 \pm 7.5	–	12.8 \pm 3.4 [12] 67.4 [19]	67.6 [19]	16.1 [39] 72.0 \pm 15.9 [42] 95.0 \pm 37.7 [37]	–	7.0 \pm 10.0 [32]	–	India: 6.5 \pm 0.5 [4] India: 6.5 \pm 3.9 [29] Netherlands: 14.7 \pm 3.2 [31] Brazil: 66.0 \pm 7.6 [15] Brazil: 67.2 \pm 7.3 [16]
Copper	Caudate nucleus	2.3 \pm 1.0	5.6 \pm 1.25 [13]	–	28.6 \pm 1.9 [17]	41.9 \pm 1.6 [38] 42.0 \pm 15.9 [37]	–	23.0 \pm 14.0 [32]	36.0 \pm 4.0 [25] 37.0 \pm 7.0 [24] 40.0 \pm 5.6 [25]	–
	Putamen	3.3 \pm 1.0	7.2 \pm 1.5 [13]	9.4 \pm 2.2 [35]	–	44.0 \pm 8.6 [37] 47.2 \pm 1.1 [38]	–	36.0 \pm 13.0 [32]	28.1 \pm 3.0 [26] 29.2 \pm 3.0 [26] 42.0 \pm 4.0 [25] 42.0 \pm 7.0 [24] 35.0 \pm 10.0 [25] 40.0 \pm 10.0 [24]	–
Globus pallidus	4.1 \pm 1.3	6.8 \pm 1.61 [13]	–	–	33.4 \pm 2.2 [38] 35.0 \pm 10.5 [37]	–	22.0 \pm 8.0 [32]	–	–	

Table 3 (continued)

	South Africa*	Austria	UK	Canada	USA	Germany	Portugal	Hungary	Other
Hippocampus	2.3 ± 1.0	–	5.1 ± 1.1 [12] 14.1 [19]	13.7 [19]	16.8 ± 3.0 [42] 27.0 ± 1.4 [38] 29.0 ± 11.2 [37]	–	19.0 ± 9.0 [32]	23.0 ± 2.0 [25]	India: 4.0 ± 1.0 [4] India: 6.4 ± 1.3 [29]
Manganese									
Caudate nucleus	0.072 ± 0.074	0.383 ± 0.075 [13]	–	3.6 ± 1.4 [17]	0.430 ± 0.026 [3] 1.4 ± 0.2 [38]	–	2.3 ± 0.7 [32]	2.5 ± 0.5 [26] 3.6 ± 0.8 [25] 3.8 ± 1.7 [24] 4.9 ± 1.3 [25]	Denmark: 0.333 [20] Belgium: 2.5 ± 0.3 [14]
Putamen	0.090 ± 0.114	0.44 ± 0.102 [13]	–	–	0.518 ± 0.014 [3] 1.9 ± 0.1 [38]	–	2.5 ± 0.8 [32]	2.7 ± 0.5 [26] 3.3 ± 0.2 [26] 3.5 ± 0.2 [26] 3.9 ± 1 [25] 4.0 ± 1.7 [24]	Denmark: 0.449 [20] Belgium: 2.7 ± 0.3 [14]
Globus pallidus	0.113 ± 0.279	0.461 ± 0.130 [13]	–	–	0.382 ± 0.239 [3] 1.4 ± 0.05 [38]	–	2.0 ± 1.2 [32]	2.3 ± 0.3 [26] 2.3 ± 0.6 [25] 4.4 ± 0.8 [24]	Denmark: 0.395 [20] Belgium: 2.180 ± 0.550 [14]
Hippocampus	0.070 ± 0.301	–	0.001 ± 0.0004 [12] 0.032 [19]	0.0272 [19]	0.285 ± 0.023 [3] 1.8 ± 0.2 [38]	–	1.2 ± 0.4 [32]	2.2 ± 0.5 [25]	Denmark: 0.218 [21]
Selenium									
Caudate nucleus	0.124 ± 0.036	–	0.430 ± 0.090 [35]	–	–	0.860 ± 0.288 [23]	–	–	Denmark: 0.135 [20]
Putamen	0.147 ± 0.034	–	0.437 ± 0.080 [35]	–	0.230 [39]	1.093 ± 0.269 [23]	–	–	Denmark: 0.211 [20]
Globus pallidus	0.124 ± 0.030	–	–	–	0.170 [39]	0.704 ± 0.171 [23]	–	–	Denmark: 0.171 [20]
Hippocampus	0.092 ± 0.027	–	0.080 ± 0.020 [12] 0.817 [19]	0.784 [19]	0.170 [39] 0.210 ± 0.092 [41]	0.857 ± 0.304 [23]	–	–	Denmark: 0.121 [20] Brazil: 0.529 ± 0.092 [16] Brazil: 0.553 ± 0.087 [15]
Calcium									
Caudate nucleus	119.4 ± 63.9	72.6 ± 13.2 [13]	326.0 ± 29.6 [35]	630.0 ± 127.0 [17]	344.7 ± 32.1 [38]	–	250.0 ± 108.0 [33]	330.0 ± 65.0 [27] 383.0 ± 9.0 [25]	Japan: 4112.0 ± 719.0 [30]
Putamen	121.9 ± 40.5	58.2 ± 8.2 [13]	–	–	296.6 ± 28.1 [38]	310.0 ± 28.0 [27]	202.0 ± 70.0 [33]	302.0 ± 65.0 [27]	Japan: 3990.0 ± 946.0 [30] Japan: 3972.0 ± 735.0 [30]
Globus pallidus	133.8 ± 72.2	63.9 ± 13.6 [13]	–	–	236.4 ± 28.1 [38]	–	256.0 ± 193.0 [33]	–	–
Hippocampus	111.4 ± 26.8	–	144.0 ± 33.5 [12] 332.0 [19]	372.0 [19]	396.8 ± 40.1 [38]	–	255.0 ± 105.0 [33]	347.0 ± 33.0 [27]	India: 120.2 ± 3.2 [29] India: 125.0 ± 51.0 [4]
Magnesium									
Caudate nucleus	20.8 ± 7.2	94.9 ± 18.6 [13]	–	530.0 ± 11.0 [17]	746.0 ± 96.5 [37]	–	567.0 ± 71.0 [33]	673.0 ± 25.0 [27] 804.0 ± 34.0 [25]	Japan: 428.0 ± 90.0 [30]
Putamen	25.4 ± 8.7	101.7 ± 27.5 [13]	–	–	739.0 ± 235.0 [37]	620.0 ± 35.0 [27]	577.0 ± 71.0 [33]	645.0 ± 65.0 [27] 690.0 ± 20.0 [26] 790.0 ± 20.0 [26]	Japan: 441.0 ± 104.0 [30]
Globus pallidus	24.3 ± 9.6	109.7 ± 34.4 [13]	–	–	626.0 ± 72.0 [37]	–	476.0 ± 54.0 [33]	–	Japan: 428.0 ± 87.0 [30] India: 116.0 ± 17.0 [4]
Hippocampus	20.9 ± 5.5	–	387.9 [19]	396.4 [19]	658.0 ± 104.5 [37]	–	588.0 ± 87.0 [33]	667.0 ± 68.0 [27]	India: 116.7 ± 19.4 [29]

Table 3 (continued)

	South Africa*	Austria	UK	Canada	USA	Germany	Portugal	Hungary	Other
Phosphorus									
Caudate nucleus	2754.6 ± 328.2	–	9.7 ± 2.7 [35]	–	–	–	–	–	Japan: 2309.0 ± 1001.0 [30]
Putamen	2894.7 ± 327.5	–	–	–	–	–	–	–	Japan: 2843.0 ± 1242.0 [30]
Globus pallidus	3348.3 ± 449.8	–	–	–	–	–	–	–	Japan: 3718.0 ± 1287.0 [30]
Hippocampus	3045.6 ± 384.7	–	10.3 ± 1.9 [35]	–	–	–	–	–	India: 1889.4 ± 86.7 [29] India: 1900.0 ± 800.0 [4]
Sodium									
Caudate nucleus	3309.6 ± 354.3	–	–	–	–	–	–	–	Japan: 56.0 ± 43.0 [30] Brazil: 7506.0 ± 1317.0 [15]
Putamen	3291.9 ± 336.3	–	–	–	–	–	–	6400.0 ± 500.0 [28]	Japan: 52.0 ± 89.0 [30]
Globus pallidus	3421.8 ± 373.6	–	–	–	–	–	–	5000.0 ± 400.0 [28]	Japan: 37.0 ± 26.0 [30]
Hippocampus	3441.2 ± 380.0	–	–	–	–	–	–	8900.0 ± 250.0 [26] 9000.0 ± 300.0 [26]	India: 2689.7 ± 206.9 [29] India: 2700.0 ± 600.0 [4] Brazil: 7986.0 ± 1427.0 [16]
Strontium									
Caudate nucleus	0.234 ± 0.082	–	–	–	–	–	–	0.155 ± 0.033 [27] 1.0 ± 0.6 [25]	–
Putamen	0.249 ± 0.092	–	–	–	–	0.310 ± 0.017 [27]	–	0.093 ± 0.023 [27] 0.8 ± 0.5 [25]	–
Globus pallidus	0.330 ± 0.124	–	–	–	–	–	–	1.0 ± 0.9 [25]	–
Hippocampus	0.262 ± 0.064	–	0.006 ± 0.002 [12] 0.224 [19]	0.184 [19]	–	–	–	0.188 ± 0.026 [27] 1.3 ± 0.5 [25]	–
Barium									
Caudate nucleus	0.056 ± 0.025	–	–	–	–	–	–	10.0 ± 2.0 [25]	–
Putamen	0.051 ± 0.031	–	–	–	–	–	–	10.0 ± 4.0 [25]	–
Globus pallidus	0.077 ± 0.043	–	–	–	–	–	–	15.0 ± 8.0 [25]	–
Hippocampus	0.048 ± 0.022	–	0.004 ± 0.001 [12] 0.264 [19]	0.325 [19]	–	–	–	10.0 ± 4.0 [25]	–
Cadmium									
Caudate nucleus	0.007 ± 0.003	–	–	–	–	–	–	–	–
Putamen	0.006 ± 0.004	–	–	–	–	–	–	–	–
Globus pallidus	0.007 ± 0.005	–	–	–	–	–	–	–	–
Hippocampus	0.006 ± 0.004	–	0.642 [19]	0.472 [19]	–	–	–	–	Netherlands: 0.021 ± 0.013 [31] India: 0.022 ± 0.005 [4]

Table 3 (continued)

	South Africa*	Austria	UK	Canada	USA	Germany	Portugal	Hungary	Other
Mercury									
Caudate nucleus	0.003 ± 0.008	–	–	–	–	–	–	–	–
Putamen	0.004 ± 0.010	–	–	–	–	–	–	–	–
Globus pallidus	0.005 ± 0.011	–	–	–	0.013 [39]	–	–	–	–
Hippocampus	0.003 ± 0.005	–	1.147 [19]	1.107 [19]	0.018 ± 0.027 [41]	–	–	–	–

Citation indicated in square brackets

UK United Kingdom, USA United States of America

*Data from the present study (wet weight). Values are expressed as median ± SD

depression, as well as altered functioning of axons [1, 12, 31], while elevated zinc levels can lead to epileptic seizures [43]. Our results were similar to reports from India [4, 29] and Canada [17]. However, most other studies had much higher zinc concentrations, such as Austria [13], Brazil [15, 16], Eastern Canada [19], Germany [22, 23], Hungary [24–26], Japan [30], Netherlands [31], Portugal [32], UK [12, 19, 35] and USA [37, 39–43]. Low zinc levels may be related to decreased dietary zinc, foods high in phytates and insufficient zinc soil levels. Foods high in zinc include meat, seafood, cereals, legumes, seeds and dairy [49]. In developing or low-income countries, plant-based complementary foods, such as cereals and legumes, are a major source of calories. These foods typically contain high levels of phytates which reduce zinc absorption [50, 51]. Moreover, zinc levels of plants are determent by the soil; zinc-deficient soil causes zinc-deficient plants [52].

Copper

Copper is important for the catalytic activity of enzymes, including ceruloplasmin, Cu/Zn superoxide dismutase (SOD), cytochrome c and dopamine β -hydroxylase [53]. Also, copper plays a role in electron transport, and dyshomeostasis could lead to ROS production [31, 53]. Copper levels range between 4.0 and 47.2 $\mu\text{g/g}$ in the literature. However, the present study noted levels between 2.3 and 4.1 $\mu\text{g/g}$. The lowest reports are from India [4, 29], Austria [13] and UK [12, 35], and the highest reports from Canada [17, 19], Portugal [32], Hungary [24–26] and the USA [37, 38, 42]. It is possible that copper levels may increase with age, although few studies have been conducted [32, 54]. Our population had a lower mean age compared with most other studies (Table 4); thus, this could account for the lower copper levels. Copper is primarily ingested through food, and high levels of copper are found in legumes, meat, seafood and cereal [49]. Diets deficient in these foods may result in low brain copper levels. Additionally, factors affecting copper absorption include high levels of hemicellulose, fructose, zinc, iron, molybdenum and tin [55].

Manganese

Manganese is a cofactor for enzymes, such as glutamine synthetase, that are essential for glial and neuronal functioning as well as neurotransmitter synthesis [56]. Additionally, manganese as well as zinc and copper, form part of SOD to reduce oxidative stress [31]. An imbalance of manganese can lead to ROS formation, and reduced manganese levels could increase susceptibility to seizures [56]. Manganese is also toxic in high amounts, typically through occupational exposure [57]. Our results are the most similar to reports from Ward and Mason [19], who investigated cadavers from Eastern Canada and the

UK. Other reports from the UK [12] were considerably lower (0.00109 $\mu\text{g/g}$) compared with all other reports, while reports from Denmark [20, 21], USA [3, 38], Austria [13], Portugal [32], Belgium [14], Hungary [24–26] and Canada [17] were higher (0.218–4.85 $\mu\text{g/g}$). Manganese is mainly consumed through food, and the highest amount is found in nuts, legumes, cereals and pineapples [58]. A diet deficient in these foods may result in lack of manganese; however, a true deficiency is uncommon [57]. High ferritin and calcium may also reduce manganese absorption [59].

Selenium

Selenium is an essential trace element that plays a vital role in the protection of brain cells against peroxidative damage, in the form of selenocysteine and selenoproteins. Glutathione peroxidase is a selenoenzyme that removes peroxides and thus decreases oxidative damage [60]. In addition, selenium dyshomeostasis has been implicated in neurodegenerative diseases [12, 16, 19, 41], brain tumours [61] and HIV infection [62]. A deficiency is more common; however, selenium toxicity (resulting in diarrhoea, hair loss, and fatigue) has also been described [63]. The concentration of selenium in the brain ranged between 0.08 and 1.093 $\mu\text{g/g}$ in the literature. Our results were similar to UK [12, 35], Denmark [20] and USA [39, 41], while reports from Brazil [15, 16], Eastern Canada [19] and Germany [64] were considerably higher. Authors have noted that selenium levels differ depending on geographical region [65, 66]. The biggest determinant is the amount of selenium in the soil, which in turn determines the amount of selenium in the food [67]. According to the Institute for Soil, Water and Climate, Agricultural Research Council, South Africa, the Western Cape has low selenium soil content [68]. Furthermore, plants with the highest levels of selenium-containing amino acids have the highest levels of selenium, such as *Allium* (onion family) and *Brassica* (mustard family) [67]. Additional factors that can influence selenium levels include high alcohol consumption and smoking [66].

Calcium

Calcium is an intracellular messenger that is vital for neuronal functioning and viability, as well as chemical and electrical stimulation [69]. There are several calcium-dependent processes in the brain, including synaptic plasticity, neurotransmission and phosphorylation [70]. Increased calcium levels can lead to DNA fragmentation and apoptosis [54], while a reduction can result in memory and learning impairments, as well as impaired neurotransmission [70]. There is a wide range of calcium concentrations reported in the literature, ranging from 58.2 to 630 $\mu\text{g/g}$. The results of Tohno et al. [30] were a great deal higher, ranging between 3972 to 4112 $\mu\text{g/g}$. The reason for these high values is unclear,

Table 4 Information on the methodology of the studies on trace element concentrations

Study	Year	Methodology	Tissue	Age (years)	Country	Number
Harrison et al. [37]	1968	AAS	DW	–	USA	28
Hock et al. [23]	1975	NAA	DW	Mean 50, 23–66	Germany	10
Larsen et al. [20, 21]	1979, 1981	NAA	WW	15–81	Denmark	5
Goldberg and Allen [38]	1981	AAS	DW	–	USA	3
Markesbery et al. [39]	1984	INAA	WW	Adult < 85	USA	28
Markesbery et al. [3]	1984	INAA	WW	Adult < 85	USA	28
Ward and Mason [19]	1987	NAA	DW	Mean 61, 52–69	Eastern Canada	30
Duflou et al. [14]	1988	PIXE	WW	7–69	Belgium	12
Thompson et al. [40]	1988	NAA	WW	Mean 70, 52–89	USA	23
Uitti et al. [17]	1989	AES, AAS	DW	Mean 70	Canada	12
Andrási et al. [26]	1990	ICP-AES, NAA	DW	65–75	Hungary	11
Corrigan et al. [35]	1991	NAA, INAA	DW	Mean 82.3 ± 7.3	UK	6
Chen et al. [18]	1993	AAS	WW	19–90	Canada	6
Corrigan et al. [12]	1993	ICP-MS	WW	Mean 78.5 ± 9.0	UK	12
Andrási et al. [25]	1994	ICP-AES, INAA	DW	65–75	Hungary	11
Andrási et al. [24]	1995	ICP-AES, INAA	DW	Mean 70	Hungary	20
Deibel et al. [42]	1996	INAA	DW	Mean 81.7	USA	11
Rajan et al. [4]	1997	ICP-AES	WW	50–60	India	8
Cornett et al. [41]	1998	INAA	WW	69–98	USA	21
Griffiths et al. [34]	1999	AAS	WW	Mean 83.3 ± 2.1	UK	6
Rao et al. [29]	1999	ICP-AES	–	–	India	4
Andrási et al. [22]	2000	INAA	DW	Mean 58, 51–73	Germany	5
Rulon et al. [43]	2000	INAA	WW	Mean 82.8 ± 1.9	USA	8
Panayi et al. [31]	2002	ICP-MS	WW	Mean 66.8 ± 17.8	Netherlands	10
Belavari et al. [28]	2004	INAA	DW	Mean 75	Hungary	5
Peltz-Csaszma et al. [27]	2005	ETAAS, ICP-OES	DW	Mean 58, 53–72	Hungary	3
House et al. [36]	2007	AAS	WW	Mean 89	USA	2
Leite et al. [16]	2008	NAA	DW	Mean 79, 51–94	Brazil	21
Tohno et al. [30]	2013	ICP-AES	DW	Mean 83.3 ± 7.5	Japan	45
Saiki et al. [15]	2013	INAA	DW	Mean 78, 51–95	Brazil	31
Krebs et al. [13]	2014	ICP-MS	WW	Mean 61, 48–81	Austria	11
Ramos et al. [7, 32]	2014	AAS	DW	Mean 71 ± 12	Portugal	42
Correia et al. [33]	2014	AAS	DW	Mean 71 ± 12	Portugal	42
Present study	2019	ICP-MS	WW	Mean 35, 19–45	South Africa	42

AAS atomic absorption spectrometry, AES atomic emission spectroscopy, DW dry weight, ETAAS electrothermal atomic absorption spectrometry, ICP-AES inductively coupled plasma atomic emission spectroscopy, ICP-MS inductively coupled plasma mass spectrometry, ICP-OES inductively coupled plasma optical emission spectrometry, INAA instrumental neutron activation analysis, NAA neutron activation analysis, PIXE particle-induced X-ray emission, UK United Kingdom, USA United States of America, WW wet weight

although it may be due to a measurement conversion error. Our results (111.4 to 133.8 µg/g) were the most similar to reports from India [4, 29], while Austria [13] had lower levels. Higher levels are reported from Canada [17, 19], USA [38], Hungary [25, 27], UK [12, 35], Germany [27] and Portugal [33]. Dietary calcium is mostly consumed through dairy products such as yoghurt, milk and cheese [46, 71]. According to Charlton et al. [72], South Africans consume less than half the recommended daily allowance of calcium. Furthermore, studies have noted that individuals from a low socioeconomic

background consume less dairy products [46]. This may be due to availability, cost, lack of power to housing and health beliefs.

Magnesium

Magnesium is essential for the proliferation of cells and calcium transport and has a role in regulating oxidative stress [73]. Moreover, magnesium homeostasis is vital for the regulation of N-methyl-D-aspartate (NMDA) receptors, which are

required for synaptic transmission and neuronal plasticity. Reduced extracellular magnesium can result in hyperexcitability of NMDA receptors and disrupted calcium transport can lead to ROS formation. Low magnesium levels have been linked to migraines, depression and epilepsy [2]. The magnesium concentration in the literature ranged between 94.9 and 804.0 $\mu\text{g/g}$, which is considerably higher compared with the levels observed in the present study (20.8–25.4 $\mu\text{g/g}$). The highest reports are from Hungary [25–27], USA [37], Germany [27], Portugal [33], Canada [17, 19], Japan [30] and UK [19], while Austria [13] and India [4] had the lowest magnesium levels. Tohno et al. [30] noted that magnesium increased with age, and most of the authors include older participants in their studies compared with the present study (Table 4). The lack of magnesium in the diets of individuals from the Western Cape may have contributed directly to the considerably lower brain levels. Studies have noted that individuals from the Western Cape consume around 228 mg of magnesium daily, which is less than the recommended daily allowance of 310 to 420 mg [72]. Developing countries and individuals with a low socioeconomic background tend to consume less minerals, vitamins, monosaturated fats and protein [46]. Foods such as cereals, rice, nuts and leafy greens are sources high in magnesium [71].

Phosphorus

Phosphorus is essential for adenosine triphosphate (ATP) production as well as the structural integrity of cells [74]. The role of phosphorus in the brain is unknown, although inorganic phosphate has been associated with premature ageing and increased ROS in a mice-model [75]. An excessive amount of phosphorus intake has been linked to bone resorption and fractures [76], while a low intake has been linked to obesity [74]. Few authors have assessed phosphorus levels in the brain. Phosphorus levels range between 1889 and 3718 $\mu\text{g/g}$ in the literature, with the exception of Corrigan et al. [35] who observed levels between 9.7 and 10.3 $\mu\text{g/g}$. This may be due to different methodology used; Corrigan et al. [35] used neutron activation analysis to detect phosphorus, while other authors used inductively coupled plasma-atomic emission spectrometry (Table 4) [4, 29, 30]. Neutron activation analysis may not be sensitive enough to detect phosphorus. Our results were similar to reports from Japan [30], while India [29] had lower levels. This may be due to less consumption of food high in phosphorus, such as meat, dairy and processed food with added phosphorus [76].

Sodium

Sodium is important for electrolyte balance and water retention. In the brain, Na^+ ions and sodium channels are crucial for the generation of nerve impulses [77], and hyponatremia can

result in neurological damage [78]. Brain sodium levels range from 2689 to 9000 $\mu\text{g/g}$ in the literature [4, 15, 16, 26, 28, 29], with the exception of Tohno et al. [30] who observed levels between 37.0 and 56.0 $\mu\text{g/g}$. The reasons for these low values are unclear, as similar methodology was used. The present study observed sodium levels similar to reports from India [4, 29], while reports from Hungary [26, 28] and Brazil [15, 16] were higher. Dietary sodium is mostly consumed as sodium chloride. Developed and developing countries get their sodium from different sources, and processed foods have the highest sodium content [79]. In South Africa, the consumption of processed food has increased in the last two decades [80], and bread is the greatest contributor to high dietary sodium intake [72].

Strontium

Strontium is associated with calcium metabolism and may play a role in bone formation [27]. The role of strontium in the brain is unknown, although high concentrations may be related to epilepsy [81]. A possible role in neurotransmission has been suggested, since strontium can replace calcium at motor end-plates and stimulate the release of acetylcholine [81]. Four studies have investigated strontium levels in the brain, and levels vary among population groups. Our results were similar to reports from Hungary [27], Germany [27], Eastern Canada [19] and the UK [19], while other studies done in Hungary [25] had higher values, and a study done in the UK [12] had lower values. Strontium is typically ingested through food, and foods containing high levels of strontium include leafy vegetables, dairy products, spices and grains [82].

Barium

Barium has no known biological function and is toxic in high doses. Limited studies have assessed barium concentrations. Our results (0.048 to 0.077 $\mu\text{g/g}$) are higher compared with reports from the UK [12], but less compared with Eastern Canada [19] and Hungary [25]. András et al. [25] noted the highest barium concentrations (10 to 15 $\mu\text{g/g}$, Table 3), and the reason for this is unclear. The authors used similar methodology and age groups compared with the other authors (Table 4); thus, this difference could be due to higher exposure. Barium is typically exposed through water, food or air pollution [83]. Brazil nuts contain remarkably high levels of barium (3000 to 4000 $\mu\text{g/g}$) [84], while water sources such as groundwater and well water may contain higher levels of barium salts [83]. Exposure of barium can cause degeneration of neurons in the inner ear, possibly through the inhibition of K^+ channels [85]. However, limited human studies have been completed.

Cadmium

Cadmium is a non-essential heavy metal that decreases neurotransmitter synthesis, increases the blood-brain barrier permeability and reduces SOD, glutathione peroxidase and catalase leading to increased oxidative damage [86]. Only three studies [4, 19, 31] could be found that have reported the cadmium concentration in the brains of healthy controls, and these were all in the hippocampus. These levels ranged from 0.021 to 0.642 $\mu\text{g/g}$; the highest concentrations were from a UK population [19]. These values were higher compared with the present studies average of $0.006 \pm 0.004 \mu\text{g/g}$. Cadmium is typically ingested through the diet and is present in tobacco smoke, which could account for the differences in population averages. It was found that crustaceans and molluscs contained high amounts of cadmium compared with other food items [87].

Mercury

Mercury is a toxic heavy metal that causes oxidative damage and neurodegeneration. Elemental, inorganic and organic mercury compounds are present, with organic methylmercury being the most concerning. Methylmercury interacts with and oxidises sulfhydryl-containing proteins and nonprotein thiols (cysteine and glutathione), altering their functioning. Sulfhydryl-containing proteins include antioxidant enzymes and neurotransmitter receptors [88]. The mercury concentration has not previously been reported in the caudate nucleus and putamen. The present study had lower levels of mercury compared with studies done in the USA [39, 41], Eastern Canada [19] and the UK [19]. Non-occupational exposure is typically through a diet high in seafood, and possibly through dental amalgams [88].

Sex Differences

There were no significant sex differences in the present study (Table 5), and limited research has been published on trace element levels in the brain concerning sex differences. Iron deficiency has commonly been noted in women [89]; however, the present study observed only a non-significant decrease in brain iron levels. Similarly, most studies found no significant difference in brain iron levels between women and men [7, 8]. Brain copper levels were only non-significantly decreased in women in our study, which is in agreement with the results of Rahil et al. [8] and Ramos et al. [32]. In contrast, serum copper levels are typically increased in women compared with men [90]. Correia et al. [33] found that females had a higher concentration of calcium compared with men, and this is in agreement with our results (20.0% increase in women, $p = .183$). No significant difference in magnesium levels has been reported [33], and this is consistent with the present

study results. Trace elements can be altered in women due to hormones, menstruation, pregnancy and contraceptives.

Oestrogen affects the serum concentration of several trace elements. In a study by Ulas and Cay [10], ovariectomized rats had decreased serum iron, calcium, copper, zinc, selenium, manganese, chromium and phosphorus. The magnesium concentration remained unchanged. With oestrogen treatment, these trace elements increased, although magnesium was unaltered. These trace element concentration changes may be related to increased renal excretion since the urinary output of trace elements decreased after receiving oestrogen [91]. Moreover, oestrogen alters the activity of hepcidin and hypoxia-inducible factor 1a; elevated oestrogen inhibits hepcidin, which alters ferroportin that permits the flow of iron from hepatocytes, enterocytes and macrophages into the blood. Hypoxia-inducible factor 1a also inhibits hepcidin [92].

Oestrogen stimulates calcium absorption; however, the exact mechanisms are unknown. It has been suggested that oestrogen modifies the vitamin D endocrine system, increases the active form of vitamin D (calciferol, 1,25-dihydroxycholecalciferol), modifies the vitamin D receptor, increases retinol levels or acts directly via the oestrogen receptor [93]. Furthermore, oestrogen also has a role in bone resorption; oestrogen suppresses RANK ligand (receptor activator of NF- κ B) induced osteoclast resorption, thus a decrease in oestrogen will increase RANK ligand production and increase bone resorption. With bone resorption, calcium and magnesium are released into the blood [94].

Iron is decreased in women due to menstrual blood loss. Harvey et al. [95] observed that iron was decreased after menstruation and that 1 mg/day of menstrual loss resulted in a 6.9- $\mu\text{g/L}$ decrease in serum ferritin. The duration of menstruation and volume of menstrual blood loss has also been associated with increased iron loss [96].

Comparing women taking contraceptives to controls, reductions in zinc, selenium and magnesium have been noted, while copper, iron, calcium and cadmium was increased. There was no change in lead, manganese and phosphorus concentration [97]. A copper increase has especially been studied, and this increase may be due to the release of copper from the copper coil in intra uterine devices [97]. Additionally, copper increases may be due to the reduction of ceruloplasmin that has been associated with contraceptive use [98]. Contraceptive use has been linked to an increase in serum iron [97], possibly due to the decreased menstrual blood loss [95]. However, the contraceptive use of the cadavers included in this study was unknown.

Brain Regional Differences

There were several significant differences between different brain regions (Table 6). Overall, the caudate nucleus and

hippocampus were the most similar, and the globus pallidus and hippocampus the most different.

It is difficult to compare regional differences with the literature, since studies have reported varied results, and do not always include all four regions studied in the present study. The regional distribution of iron is consistent with the literature [7, 37, 38]; the highest concentration was observed in the globus pallidus, and the lowest in the hippocampus. Zinc had the highest concentration in the globus pallidus, and the lowest in the caudate nucleus. This is inconsistent with the literature; most authors observed the highest concentration in the hippocampus, and lowest in the globus pallidus [23, 32, 37]. Most literature [25, 32, 37, 38] observed the highest copper in the putamen, and the lowest in the hippocampus. However, the present study observed the highest in the globus pallidus and the lowest in the caudate nucleus. Most studies [3, 20, 21, 25, 32, 38, 39] observed the highest and lowest manganese concentrations in the putamen and hippocampus, respectively. However, the present study observed the highest manganese level in the globus pallidus, and the lowest in the hippocampus.

Selenium, calcium, magnesium, barium and strontium have seldom been investigated in all four regions. Selenium was highest in the putamen and lowest in the hippocampus, which is consistent with the literature [20, 23]. Calcium was mostly uniformly distributed, which is consistent with the results of Correia et al. [33]; however, Goldberg and Allen [38] observed a high calcium level in the hippocampus and a low concentration in the globus pallidus. Literature on magnesium distribution is still lacking and contradicting [33, 37]; the present study observed high levels in the putamen and low levels in the caudate nucleus. Barium was highest in the globus pallidus and lowest in the hippocampus, which is consistent with the literature [25]. Strontium levels were high in the globus pallidus and low in the caudate nucleus. Only one other study included all four regions and found the highest strontium levels in the hippocampus and the lowest in the putamen [25].

Phosphorus, sodium, cadmium and mercury have not been investigated in all four regions in healthy brains. In the present study, sodium levels were highest in the hippocampus, and lowest in the putamen. Cadmium was uniformly distributed. Phosphorus and mercury levels were highest in the globus pallidus and lowest in the caudate nucleus.

Various studies have noted the regional distributions of trace elements. The reason for this is still unclear, possibly related to the function of the different regions [11]. Different trace elements are involved in different metabolic actions, such as increased iron in regions of motor function [22]. Iron is crucial for myelination, which can account for higher iron levels in white matter regions [99]. Metallothionein is vital for copper, zinc and manganese homeostasis, and is located in the cytosol and thus higher in grey matter regions

Table 5 Comparison between male and female trace element concentrations ($\mu\text{g/g}$ wet weight)

	Female Median \pm SD	Male Median \pm SD	<i>p</i> value
Iron	47.6 \pm 31.170	55.5 \pm 37.5	0.687
Zinc	6.6 \pm 1.4	7.1 \pm 21.1	0.710
Copper	2.5 \pm 1.604	3.0 \pm 1.2	0.367
Manganese	0.091 \pm 0.102	0.087 \pm 0.256	0.549
Selenium	0.116 \pm 0.028	0.125 \pm 0.040	0.841
Calcium	136.1 \pm 56.5	113.4 \pm 52.0	0.183
Magnesium	21.3 \pm 5.3	24.0 \pm 9.0	0.207
Phosphorus	2893.5 \pm 318.0	3054.4 \pm 469.1	0.678
Sodium	3258.0 \pm 283.1	3372.5 \pm 386.3	0.171
Strontium	0.281 \pm 0.064	0.263 \pm 0.114	0.480
Barium	0.060 \pm 0.029	0.051 \pm 0.035	0.543
Cadmium	0.008 \pm 0.005	0.007 \pm 0.003	0.341
Mercury	0.005 \pm 0.009	0.003 \pm 0.009	0.130

[31]. Manganese is also bound to glutamine synthetase in astrocytes [100]. Zinc is stored as zinc metalloproteins in glial cells and neurons, or as ionic zinc in synaptic vesicles [101]. Additionally, zinc may be increased in the hippocampus due to its role as a neuromodulator [22], although this was not observed in the present study. Copper is higher in glial cells compared with neurons, specifically periventricular glial cells possibly due to the proximity to the cerebrospinal fluid [102]. Selenium tends to be more concentrated in grey matter and glandular regions, although the reason is unclear [60].

The number of blood vessels present in a brain region could affect the concentration of trace elements. The caudate nucleus and putamen have denser microvascular regions compared with the globus pallidus [103], and it has been reported that grey matter is more densely supplied compared with white matter regions [104]. Calcification of blood vessels with age may also impact the trace element levels. Larsen et al. [20] included considerably younger participants (range 15 to 81 years) compared with Ramos and colleagues [7, 32, 33] (range 53 to 101 years, mean 71) and András et al. [25] (range 65 to 75 years). The results of Larsen et al. [20] was comparable with the results of Ramos and colleagues [7, 32, 33]; however, the discrepancies could possibly be due to the varying age ranges included by András et al. [25], Goldberg and Allen [38] and Harrison et al. [37]. Age has been noted to alter trace element concentrations, and that these alterations may become more pronounced in certain regions.

Limitations

Limitations for this study include that the medical history of the cadavers is not available; thus, any existing

Table 6 Significant differences in trace element concentrations between the caudate nucleus, putamen, globus pallidus and hippocampus ($\mu\text{g/g}$ wet weight)

	Caudate nucleus	Putamen	Globus pallidus	Hippocampus	Overall <i>p</i> value	
Iron	47.1 \pm 18.4	65.5 \pm 28.6	103.2 \pm 32.1	23.6 \pm 11.5	0.001	A, B, C, D, E, F
Zinc	5.5 \pm 2.6	6.8 \pm 25.7	8.4 \pm 22.8	6.1 \pm 7.5	0.001	A, B, D, e, F
Copper	2.3 \pm 1.0	3.3 \pm 1.0	4.1 \pm 1.3	2.3 \pm 1.0	0.001	A, B, D, e, F
Manganese	0.072 \pm 0.074	0.090 \pm 0.114	0.113 \pm 0.279	0.070 \pm 0.301	0.001	B, d, F
Selenium	0.124 \pm 0.036	0.147 \pm 0.034	0.124 \pm 0.030	0.092 \pm 0.027	0.001	A, C, D, E, F
Calcium	119.4 \pm 63.9	121.9 \pm 40.5	133.8 \pm 72.2	111.4 \pm 26.8	0.012	f
Magnesium	20.8 \pm 7.2	25.4 \pm 8.7	24.3 \pm 9.6	20.9 \pm 5.5	0.001	A, B, e, f
Phosphorus	2754.6 \pm 328.2	2894.7 \pm 327.5	3348.3 \pm 449.8	3045.6 \pm 384.7	0.001	a, B, C, D, e, F
Sodium	3309.6 \pm 354.3	3291.9 \pm 336.3	3421.8 \pm 373.6	3441.2 \pm 380.0	0.001	d
Strontium	0.234 \pm 0.082	0.249 \pm 0.092	0.330 \pm 0.124	0.262 \pm 0.064	0.001	B, c, D, F
Barium	0.056 \pm 0.025	0.051 \pm 0.031	0.077 \pm 0.043	0.048 \pm 0.022	0.001	b, D, F
Cadmium	0.007 \pm 0.003	0.006 \pm 0.004	0.007 \pm 0.005	0.006 \pm 0.004	0.448	–
Mercury	0.003 \pm 0.008	0.004 \pm 0.010	0.005 \pm 0.011	0.003 \pm 0.005	0.001	a, B

Letter A indicates significant difference at $p < 0.001$ between caudate nucleus and putamen; letter a indicates significant difference at $p < 0.05$ between caudate nucleus and putamen; letter B indicates significant difference at $p < 0.001$ between caudate nucleus and globus pallidus; letter b indicates significant difference at $p < 0.05$ between caudate nucleus and globus pallidus; letter C indicates significant difference at $p < 0.001$ between caudate nucleus and hippocampus; letter c indicates significant difference at $p < 0.05$ between caudate nucleus and hippocampus; letter D indicates significant difference at $p < 0.001$ between putamen and globus pallidus; letter d indicates significant difference at $p < 0.05$ between putamen and globus pallidus; letter E indicates significant difference at $p < 0.001$ between putamen and hippocampus; letter e indicates significant difference at $p < 0.05$ between putamen and hippocampus; letter F indicates significant difference at $p < 0.001$ between globus pallidus and hippocampus; letter f indicates significant difference at $p < 0.05$ between globus pallidus and hippocampus.

neurodegenerative diseases are unknown. Most of these diseases are present in older individuals; therefore, the sample size only included individuals under the age of 45. Possible neurological diseases that are present in younger individuals (depression, schizophrenia) could not be excluded. Formalin may cause leaching of trace elements; thus, samples must be analysed as soon as possible. Moreover, only the last known resident area of the individuals is known. The cadavers are thus only a representative of a Western Cape cadaver cohort. Lastly, comparison of literature using different metal analysing methods is difficult, as different methods may have dissimilar sensitivities.

Conclusion

In summary, this is the first article to report the trace element concentrations of brain regions from a South African population of the Western Cape. Trace element concentrations in the brain are varied in the literature, and the present study's results were typically comparable with other population groups, such as India, UK and Canada. However, the magnesium levels were considerably lower compared with reported values from the literature. There was no significant sex difference for trace element concentrations; however, several regional differences were observed in the brain. Regional distribution of iron, selenium and barium were consistent with the literature, while

zinc and manganese were only partially consistent with previous reports. Copper, calcium, magnesium and strontium were inconsistent with the literature, and this is the first article to report the concentrations of phosphorus, sodium, cadmium and mercury in all four brain regions (caudate nucleus, putamen, globus pallidus and hippocampus). Low magnesium levels in the brain may be linked to a dietary deficiency, and migraines, depression and epilepsy have been linked to low magnesium levels. Future research should be directed to increase dietary intake magnesium.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Health Research Ethics Committee, Stellenbosch University, S17/09/183) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the Legally Authorized Representative or from the next of kin.

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