Age related brain atrophy may be mitigated by internal jugular vein enlargement in male individuals without neurologic disease

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Abstract

Objectives: To assess the relationship between cross-sectional area (CSA) of internal jugular veins (IJVs) and brain volumes in healthy individuals without neurologic disease (HIwND).

Methods: 193 HIwNDs (63 male and 130 female; age <20 to >70 years) received magnetic resonance venography and structural brain MRI at 3T. The IJV-CSA was assessed at C2-C3, C4, C5-C6, and C7-T1. Normalized whole brain volume (NWBV) was assessed. Partial correlation analyses were used to determine associations.

Results: There was an inverse relationship between NWBV and total IJV-CSA (C7-T1: males r= -0.346, p=0.029; females r= -0.301, p=0.002). After age adjustment, association of NWBV and normalized gray matter volume with IJV-CSA became positive in males (NWBV and right IJV-CSA (C2-C3) changed from r = -0.163 to r = 0.384, p=0.002), but not in the females.

Conclusion: Sex differences exist in the relationship between brain volume and IJV-CSA in HIwND.

Introduction

Recently a large epidemiological study involving nearly 2 million subjects, demonstrated an association between increased body mass index (BMI) and a reduced risk of dementia in old age. [1] This counter-intuitive finding, which contradicts previous thinking on the subject, [2] prompts investigation of the pathophysiological mechanisms linking changes in the brain with changes in the thorax and the abdomen. While the nature of these mechanisms is unknown, it has been observed that widening of the internal jugular vein (IJV) lumen is frequently associated with jugular venous reflux (JVR) in the elderly, [3] and that this is associated with increased brain parenchymal volume in patients with Alzheimer's disease. [4] It has also been demonstrated that increased BMI is associated with enlarged IJVs both in healthy individuals and patients with multiple sclerosis (MS). [5] Collectively, these findings raise intriguing questions as to whether or not changes in the cerebral venous drainage system, associated with increased BMI, might mitigate the effects of brain atrophy associated with aging. [6]

It is known that constricted cerebral venous outflow is linked with increased aqueductal cerebrospinal fluid pulsatility in healthy individuals [7] and that this in turn is thought to be associated with early stage white matter damage build-up in the brain parenchyma. [8] It can therefore be postulated that physiological cerebral venous drainage, characterized by larger IJVs, might be associated with reduced brain atrophy in aging, while narrowing of the IJVs might be associated with more severe brain atrophy. We therefore designed the study presented here, in which we performed magnetic resonance imaging (MRI) of the brain and magnetic resonance venography (MRV) of the left and right IJVs at levels C2-C3, C4, C5-C6 and C7-T1 in 193 healthy individuals without neurologic disease (HIwND) of various ages. The aim of the study was to characterize the relationship between brain volumes and IJV cross-sectional area (CSA) in both male and female subjects and evaluate the effect of aging on this relationship.

Materials and methods

Subjects and Clinical Data:

This prospective, single-center, cross-sectional study included 193 consecutive HIwND (63 male and 130 female; age range <20 to >70 years) who were part of an ongoing prospective study of cardiovascular, environmental and genetic risk factors in MS that enrolled over 1,000 subjects with MS, HIwND and patients with other neurologic diseases. [9, 10] Inclusion criteria included completion of MRI screening to ensure no MRI-prohibitive medical history. Subjects also needed to complete a health screening questionnaire containing information about medical history (illnesses, surgeries, medications, etc.) and were required to meet the health screening requirements on physical

examination. History of known vascular abnormalities precluded enrollment in the study. Cardiovascular risk factors including a history of heart disease, hypertension and smoking werre collected. Recruited subjects included hospital personnel, local advertisement respondernts, and spouses/relatives of clinical patients receiving care at our center. All participants underwent clinical and MRI examinations in accordance with the relevant guidelines and regulations. The study was approved by the University of Buffalo Institutional Review Board and written informed consent was obtained from all subjects.

Image Acquisition:

All subjects were examined on a GE 3.0T Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, GE, Milwaukee, WI) with a maximum slew rate of 150T/m/s and maximum gradient amplitude in each orthogonal plane. A 2-dimensional Magnetic Resonance Venography (MRV) sequence was acquired for all jugular CSA measurements. This MRV was run with 150 1.5mm-thick slices using a 320x192 matrix (frequency x phase) with a 22.0 cm field of view (FOV) and a phase field of view (pFOV) of 75% for a resolution of .69 x 1.15 x 1.5 mm^3. Additional imaging parameters included Echo Time (TE) / Repetition Time (TR) / Flip Angle (FA) of 4.3 ms / 14 ms / 70°, and a Bandwidth (BW) of 31.25 kHz, for a total acquisition time of 5:19. MRV was acquired in a “true” (non-obliqued) axial orientation with one average, and no parallel imaging techniques were employed. We also acquired a 3D T1-weighted fast spoiled gradient-echo with magnetization-prepared inversion recovery for the brain volume measurements. We collected 128 1.5mm-thick slices using a 256x256 matrix with a 25.6 cm FOV with a pFOV of 75%, TR/TE/Inversion Time of 5.9 ms/2.8 ms/ 900 ms, and FA of 10°.

In a subset of 33 subjects (29 females and 4 males) with an average age of 49.9 years (SD = 13.2 year), and in order to assess the relationship between CSA and venous blood flow in the IJVs, we acquired 2D phase-contrast (PC) MR scan for flow quantification. The PC-MRI was acquired perpendicular to the IJVs at the neck levels C2-C3 and C7-T1. We used 2.5mm-thick slices using a 320x192 matrix (frequency x phase) with a 22.0 cm FOV and a pFOV of 75% for a resolution of 0.69 x 0,.69 x 2.5 ^{m}m3. Additional imaging parameters included TE 9.9, TR 40, FA 20°, and a B) of 530 kHz, for a total acquisition time of 4:15. A maximum encoding velocity (VENC) of 20cm/sec was used for PC-MRI. MRV was acquired in a transverse orientation and no parallel imaging techniques were employed.

MRI analyses:

Internal jugular vein cross-sectional analysis:

IJV assessment was performed on the subjects in the supine position using CSA region of interest (ROI) analysis on the 2D MRV with the semi-automated contouring technique (Interactive Contours ROI display of the Java Image Manipulation Tool version 5.0, http://www.xinapse.com) at specific

neck locations. This interactive tool enables adjustment of the ROI to the irregularity of the IJV shape at various neck levels, to ensure the most accurate segmentation. Briefly, the sequence was viewed orthogonally to assess which slices corresponded to the desired anatomical coverage, namely C2-C3, C4, C5-C6, and C7-T1. Within each of these locations, the operator determined the slice on which the IJV came to a minimum, and then outlined the right and left IJVs. An example case showing each of the four neck levels with the IJV ROI's indicated is presented in Figure 1.

Reproducibility of the IJV CSA analysis was assessed using two operators on a set of 25 MRVs twice, with analyses a minimum of 2 weeks apart. Three operators were blinded to each other's ROI assessments, as well as to their own prior set of ROIs. Intra- and inter-operator reproducibility was assessed using the Intra-class Correlation (ICC).

Internal jugular vein blood flow rate analyses:

Additional *post hoc* analysis was performed on a subset of 33 individuals from the study cohort using flow rate data acquired at neck levels C2-C3 and C7-T1. Blood flow rates of IJVs were measured using software written in MATLAB (The Mathworks, Natick, MA) to quantify blood flow through major arteries and veins, as previously reported (SPIN version 2205., www.mrc.wayne.edu/download.htm). [11-13] Briefly, both the magnitude and phase images were viewed, drawing IJV ROI's upon the magnitude image for clear outlining and the phase image as a reference for the direction of the flow. The operator first determines a no-flow area as a degree of error to account for imaging noise, followed by drawing ROI's of the each of the IJVs at both the C2/C3 and C7-T1 levels. The ROI's were obtained through all of the remaining magnitude and phase images and subsequently IJVs flow rate were obtained.

Brain atrophy analyses:

The *Structural Image Evaluation using Normalization of Atrophy* (SIENAX) cross-sectional software tool (version 2.6;http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) was used for brain extraction and tissue segmentation, with correction for T1-hypointensity misclassification. [14] We obtained the following volume measures: normalized whole brain (NWBV), normalized gray matter volume (NGMV), normalized white matter volume (NWMV), normalized cortical volume (NCV) and normalized lateral ventricle volume (NLVV).

Statistical Analysis:

Statistical analyses were performed using the Statistical Package for Social Sciences (IBM Inc, version 21.0). The demographic and clinical differences between males and females were tested using Student's *t*-test and chi-square tests. Pearson correlation analysis comparing age with IJV CSA was performed for both sexes with the cardiovascular risk factors, used as covariates. A two-tail test using Fisher's r-to-z transformation was used to test the significance of any changes in

correlated r-values. Pearson correlation analysis was performed, *post hoc*, on subset of subjects from the study cohort to compare IJV CSA and blood flow rate in the caudal direction at neck levels C2-C3 and C7-T1.

Due to multiple comparisons, only p-value <0.01 were considered statistically significant using a two-tailed test, while p-values <0.05 were considered to represent a statistical trend.

RESULTS

Demographic and clinical characteristics:

The demographic and clinical characteristics are presented in Table 1. The average age of the male subjects was 40.7 years (SD = 17.1 years), with that of the females being 44.1 years (SD = 17.7 years). Analysis of the clinical characteristics revealed no significant sex-related differences for cardiovascular risk factors or any of the normalized brain volume measures. Trends were observed towards larger IJV CSAs on the right hand side in the males compared with the females at levels C4 and C7-T1.

Reproducibility:

A high degree of inter- and intra-operator IJV CSA reproducibility was observed, with strong ICC values (ICC>0.69 for inter-operator and ICC>0.84 for intra-operator, both p<0.001) found at all neck levels for all operators.

Correlation results:

As expected, the correlation analysis revealed decreased brain volumes in both sexes to be associated with aging. Strong negative correlations of similar magnitude were observed between increased age and reduced NWBV in both males (r = -0.735, p<0.001) and females (r = -0.696, p<0.001), with the effect more pronounced for NGMV (males, r = -0.800, p<0.001; females, r = -0.792, p<0.001), than NWMV (males, r = -0.398, p=0.003; females, r = -0.298, p=0.001). Conversely, a positive relationship was found between increased age and enlarged NLVV (males, r = 0.623, p<0.001; females, r = 0.406, p<0.001).

A positive relationship was also observed between increased age and enlarged IJV CSA in the lower neck, which was stronger in the males (at C7-T1: left IJV, r = 0.444, p<0.001; right IJV, r = 0.413, p=0.001) than the females (at C7-T1: left IJV, r = 0.209, p=0.017; right IJV, r = 0.244, p=0.005). In the upper neck (C2-C3), while this positive relationship was maintained in the males (left IJV, r = 0.263, p=0.037; right IJV, r = 0.462, p<0.001), it was not present in the female subjects (left IJV, r = 0.035, p=0.692; right IJV, r = 0.019, p<0.830).

BMI was positively correlated with age in both the males (r = 0.301, p=0.036) and females (r = 0.267, p=0.004), highlighting the tendency of the subjects to put on weight as they aged. BMI was

negatively correlated with NWBV in both the males (r = -0.327, p=0.023) and females (r = -0.205, p=0.028), with a similar effect observed for NGMV (males: r = -0.260, p=0.074; females: r = -0.271, p=0.003) and NCV (males: r = -0.255, p=0.080; females: r = -0.253, p=0.006). Interestingly however, there was a marked difference in the correlation between BMI and NWMV for the males (r = -0.309, p=0.033) and the females (r = -0.034, p=0.716).

The results of the partial correlation analysis with cardiovascular risk factors, as covariates, are presented in Table 2, which shows the correlations between the MRI brain volume variables and the MRV IJV CSA variables. These results reveal some clear trends and patterns, chief of which is that almost all the correlations between brain volumetric variables and the IJV variables were negative. The main exceptions to this, are relationships with NLVV which were predominantly positive. This implies that as CSA of the IJVs increased, so the volume of the brain tended to decrease and the volume of the lateral ventricles increase. This phenomenon was particularly strong with respect to the IJVs in the lower neck. For example, at C7-T1 the correlation between NWBV and the left IJV CSA was (males, r = -0.400, p=0.011; females, r = -0.226, p=0.019), while that for the right IJV CSA was (males, r = -0.226, p=0.160; females, r = -0.287, p=0.003). Interestingly, while the correlations for the male and female subjects were of similar strength in the lower neck (C5-T1), marked sex-related differences were observed in the upper neck (C2-C4), with the correlations relating to the females becoming much weaker at these levels.

Correlation results adjusted for age:

In both males and females there was a general trend towards a positive relationship between increased BMI and enlarged IJVs. However, with respect to this there were marked sex-related differences. When we controlled for age and cardiovascular risk factors, we found that the correlations between BMI and IJV CSA in the male subjects only achieved significance on the left hand side (at C7-T1: left IJV, r = 0.434, p=0.009; at C5-C6: left IJV, r = 0.428, p=0.010; at C4: left IJV, r = 0.476, p=0.004; at C2-C3: left IJV, r = 0.416, p=0.013), while the correlations for the right IJV were much weaker (at C7-T1: right IJV, r = -0.020, p=0.909; at C5-C6: right IJV, r = 0.041, p=0.816; at C4: right IJV, r = -0.009, p=0.959; at C2-C3: right IJV, r = -0.101, p=0.563). By comparison in the females, the effect was less strong, bilateral, and confined to the lower neck (at C7-T1: left IJV, r = 0.177, p=0.075; right IJV, r = 0.201, p=0.042; at C5-C6: left IJV, r = 0.179, p=0.071; right IJV, r = 0.115, p = 0.251; at C4: left IJV, r = 0.085, p=0.396; right IJV, r = 0.013, p = 0.898; at C2-C3: left IJV, r = 0.063, p=0.527; right IJV, r = -0.043, p = 0.665).

When the correlation analysis between IJV CSA and brain volume was performed with age included as one of the covariates (Table 3), the results changed markedly, as the analyses in Tables 2 and 3 reveal. Many of the correlations between the brain MRI variables and IJV CSA weakened in the female subjects. When controlling for age, positive correlations were still observed in the females with regard to NLVV, whereas the males showed a reversal in the direction

of this correlation for the right IJV CSA at almost all levels. As such, this indicates that when co-varying for age in the female subjects, there was still an inverse relationship between IJV CSA and brain volume, with one increasing and the other decreasing - although this relationship was generally slightly weaker than was the case when age was not included in the covariates. On the contrary, in male subjects, many correlations involving NWBV, NGMV and NCV that were negative before controlling for age, became positive after age was included in the covariates. For example, before controlling for age the relationship been NCV and the right IJV CSA in the males was r = -0.230 (p=0.154) at C5-C6 and r = -0.221 (p=0.171) at C2-C3, whereas after age was included as a covariate these relationships became r = 0.289 (p=0.074) and r = 0.398 (p=0.012), respectively – changes that were strongly significant (p=0.004 and p<0.001) when assessed using Fisher's r-to-z transformation. In males, this phenomenon was observed at all neck levels, predominantly on the right hand side, implying that when the effects of aging were eliminated, in these subjects, NWBV, NGMV and NCV all tended to increase as IJV CSA increased.

Table 4 shows the results of using Fisher's r-to-z transformation to assess the significance of the changes in key correlations arising from the inclusion of age as a covariate. These reveal a profound difference between the sexes when age-related effects are eliminated. While in the males most of the changes in correlations relating to NWBV, NGMV, NLVV and NCV were significant or trending towards significance, none of the corresponding z values for the females reached significance.

Post hoc evaluation of internal jugular vein flow rate verses cross-sectional area:

Post hoc analysis revealed significant positive correlations between IJV flow rate and IJV CSA at levels C2-C3 (left: r = 0.561, p = 0.001; right: r = 0.610, p < 0.001) and C7-T1 (left: r = 0.529, p = 0.002; right: r = 0.536, p = 0.001), indicating that larger IJV CSAs were indicative of increased IJVs flow rate in the caudal direction.

Discussion

Our findings indicate that in both males and females, IJV CSA in the lower neck increases as age increases, confirming Chung et al. [3] who observed in elderly individuals that the IJV lumen frequently becomes distended. We also found that the IJVs enlarge as BMI increases, in a relationship independent of age, just as Magnano et al. observed. [5] As such, our findings suggest that the IJV CSA is indicative of changes in BMI.

Given that brain atrophy and IJV CSA both increase with age, it is not surprising that, when age was omitted from the covariates, we found inverse correlations between brain volume and IJV CSA in both male and female subjects (Table 2) - a phenomenon that was strongest with respect to the

lower neck (C5-T1). However, after controlling for age (Table 3), many of these negative correlations became positive in the male subjects. This effect was consistent and occurred at all neck levels, and was most pronounced for the right IJV (Table 4). As such, this implies that in the male subjects, after allowing for brain atrophy due to aging, NGMV and NCV tended to increase as the right IJV CSA increased, mirroring the phenomenon observed in Alzheimer's patients. [4] By comparison, the same phenomenon was not observed in the female subjects.

While we did not investigate neuropsychological status of the subjects, our results may shed light on the findings of Qizilbash et al. [1] who observed that obese individuals had a lower risk of contracting dementia compared with people of a healthy weight. Dementia in elderly individuals is associated with increased rates of brain atrophy [15] and in particularly with enlarged lateral ventricles. [16] We found that, after controlling for age and cardiovascular risk factors, larger IJVs appeared to mitigate the effects of gray matter (NGMV and NCV) atrophy (Table 4). Furthermore, in males, the direction of the correlation between NLVV and the IJV CSA's inverted once age was included as a covariate, implying that increased IJV CSA was associated with smaller ventricles, with a more pronounced effect for the right IJV at the upper neck levels. Although these results appear to support those of Qizilbash et al., it is important to note that these findings were restricted only to the males. In female subjects, the inclusion of age as a covariate made relatively little difference to the respective correlations, with those between NLVV and the IJV CSAs in particular remaining positive. Therefore, caution should be exercised when comparing our results with those previously reported. [1]

The difference between the sexes is starkly highlighted in Table 4. In females, after controlling for age, the inverse relationship between brain volume and increased IJV CSA still remained, albeit at reduced strength, with none of the corresponding r-to-z transformations reaching significance. While the correlations between age and brain volume revealed little difference between the males and females, it is noticeable that profound differences between the sexes were observed in the correlations between age and IJV CSA in the upper neck, suggesting that the observed differences related to changes at this location. The IJVs in the upper neck are covered over by the sternocleidomastoid muscles, which are much thicker in males than in females. [17] Sarcopenia (muscle wasting) associated with aging can greatly influence both muscle thickness and muscle structure, [18-20] with males exhibiting a much greater degree of sarcopenia in the sternocleidomastoid muscles as they age compared with females. [17] Sex-related differences in the musculature of the neck may therefore explain the observed differences between the sexes in the relationship between brain volume and IJV CSA. BMI is a strong predictor of skeletal muscle mass in males and females, and it has been shown to correlate strongly with sarcopenia. [21] Muscle and fat mass are strongly interconnected from a physiological and pathogenetic point of view. Aging and increased BMI have both been shown to greatly influence IJV CSA, [17] and in turn brain volume measures. Further investigation is needed into the relationship between the sarcopenia of the

sternocleidomastoid muscle and the IJVs to determine if this could be a contributing factor to changes in brain volume with age.

Why increased IJV CSA should mitigate loss of brain volume in males is difficult to explain. One possible explanation might be that enlarged IJVs in the neck are indicative of vessel constriction further down stream; with the result that venous blood is retained in the thin-walled cortical veins in the cranium, causing the NWBV to increase. If venous blood were retained in the cranium, then one would expect this phenomenon to be observed most acutely in the cortical and total gray matter, which is exactly what we found in the male subjects, where a positive relationship was observed between IJV CSA and NGMV and NCV, but not with NWMV. However, since we found no evidence of vessel constriction, it is more likely that enlarged IJVs were indicative of increased venous blood flow, something that appears to be confirmed by the results of the *post hoc* correlation analysis which found larger CSAs to be associated with increased IJV flow rate in the caudal direction. In which case, it can be postulated that the positive relationship between IJV CSA and NWBV might be due to increased blood flow through the cortical veins, and improved perfusion of the cortical gray matter. Conversely if the IJVs narrow, then this may be indicative constricted cerebral venous drainage and poor perfusion of the cortical gray matter, something that might cause brain atrophy to accelerate. Given that IJVs play an influential role in cerebral venous drainage, particularly when supine, [22] narrowing of these vessels will tend to increase the overall hydraulic resistance of the venous pathways back to the heart, something that will reduce blood flow and may also result in raised venous pressure in the dural sinuses. [23] [24] Regardless, further investigations will be required to better understand the physiological processes at work.

While the discussion above evaluates possible mechanisms linking increased IJV CSA with reduced loss of brain volume, it does not explain why males should exhibit this phenomenon and not females. Although it is known that the carotid arteries tend to be larger in males than in females, [25] relatively little is known about the differences between the sexes regarding the veins in the neck, or indeed how the neck veins alter with age. Our finding that IJV CSA in the upper neck increased with aging in the males, but not in the females, suggests that the differences that exist are associated with this location. Although we did not investigate the rerouting of blood in the present study, it may be that other collateral venous pathways adapt to compensate for the physiological changes that occur in females during aging, whereas in males these age related changes might be more restricted to the IJVs. Aging is known to be associated with changes in the position of the IJVs relative to the carotid arteries in both sexes. [26] It is also associated with an increased incidence of JVR [3] While most IJVs contain valves to protect against JVR, it has been shown that these are frequently incompetent, with the result that retrograde flow can readily occur if the central venous pressure becomes too high. [27] As the IJVs enlarge with age, it is thought that the valves become less competent leading to increased JVR. [3] While we found enlarged IJV CSA to be generally associated with increased venous blood flow in the caudal direction, we cannot rule

out the possibility that the JVR may have contributed to the reduction in apparent brain atrophy that we observed in the male subjects. Indeed, JVR has been shown to be associated with increased brain volume in patients with Alzheimer's disease. [4] Given that the IJVs on both sides of the upper neck enlarged with age in the males, it may be that this makes the male subjects more prone to JVR than the females. Further investigations will therefore be required to evaluate the contribution of JVR to the gender related differences that we observed.

The HIwND enrolled in the study were part of the baseline data from an ongoing prospective study into cardiovascular, environmental and genetic risk factors in MS. [9, 10] Given that the prevalence of MS is higher in females, our HIwND cohort was skewed toward more females than males, which is an important limitation of this study. Therefore it is necessary to confirm our findings in larger sample of male subjects. In addition, we did not explore the relationship between IJV CSA and brain volume in relation to cognitive impairment, level of hydration, carotid and vertebral arteries stenosis or thyrotoxic goitre. These conditions may have potentially influenced on our findings. We therefore recommend that our findings should be confirmed in a multicentre study.

In conclusion, our findings indicate that although there is a general inverse relationship between brain volume and IJV CSA in HIwND, when age is controlled for, this relationship disappears in males, but not in females. Specifically, when accounting for age, we found a positive relationship in males between IJV CSA and NGMV and NCV. This implies that efficient cerebral venous drainage, typified by larger IJVs, may mitigate the effects of age-related brain atrophy, while constricted venous outflow might promote brain atrophy, although the physiological reasons for this are unknown. Profound differences were observed between males and the females, which may be associated with JVR, sarcopenia of the sternocleidomastoid muscles, IJV valves and other medical conditions, although further work will be required to verify this.

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Table 1. Descriptive statistics of the demographic, cardiovascular risk factor, MRI brain volume and magnetic resonance venography data.

Sex (M/F)	Total (N=193)	Male (N=63)	Female (N=130)	p-value
Age mean (SD) (Years)	43.0 (17.5)	40.7 (17.1)	44.1 (17.7)	0.210
Heart Disease n (%)	20 (12.3%)	5 (10.6%)	15 (12.4%)	0.770
Hypertension n (%)	19 (11.2%)	6 (12.2%)	13 (10.8%)	0.790
Smoking n (%)	58 (32.2%)	16 (29.6%)	42 (33.3%)	0.630
BMI mean (SD) (kg/m^2)	26.8 (5.7)	27.6 (26.6)	26.5 (24.7)	0.370
NWBV mean (SD) (mL)	1535.9 (91.6)	1537.8 (95.3)	1535.1 (90.4)	0.860
NGMV mean (SD) (mL)	782.5 (63.1)	776.2 (64.5)	785.2 (62.9)	0.380
NWMV mean (SD) (mL)	753.4 (45.2)	761.6 (46.5)	749.9 (44.3)	0.110
NLVV mean (SD) (mL)	33.4 (14.8)	36.4 (15.9)	32.1 (14.2)	0.076
NCV mean (SD) (mL)	637.6 (54.2)	630.9 (55.6)	640.6 (53.5)	0.270
Right C7–T1 IJV CSA mean (SD) (mm^2)	68.7 (53.7)	82.0 (54.2)	62.3 (52.4)	*0.016*
Left C7–T1 IJV CSA mean (SD) (mm^2)	49.3 (37.5)	52.2 (40.2)	47.8 (36.2)	0.453
Right C5–C6 IJV CSA mean (SD) (mm^2)	55.4 (38.0)	62.6 (41.8)	51.9 (35.6)	0.066
Left C5–C6 IJV CSA mean (SD) (mm^2)	42.1 (30.6)	43.7 (33.1)	41.3 (29.5)	0.603
Right C4 IJV CSA mean (SD) (mm^2)	52.5 (28.2)	59.5 (31.7)	49.0 (25.7)	*0.016*
Left C4 IJV CSA mean (SD) (mm^2)	38.8 (23.5)	42.0 (26.0)	37.2 (22.0)	0.188
Right C2–C3 IJV CSA mean (SD) (mm^2)	39.2 (24.1)	41.6 (25.4)	38.0 (23.5)	0.298
Left C2–C3 IJV CSA mean (SD) (mm^2)	27.5 (18.0)	28.0 (19.0)	27.2 (17.6)	0.789

Legend: M-males; F-females; SD-standard deviation; n-number; BMI=Body Mass Index; NWBV-normalized whole brain volume; NGMV-normalized gray matter volume; NLVV-normalized lateral ventricle volume; NCV-normalized cortical volume; IJV-internal jugular vein; CSA-cross-sectional area.
p-values were calculated using Student's T-Test and chi-square tests, with values less than 0.01 considered significant **(bold)**. p-values less than 0.05 were considered trends *(italics)*.

Table 2. Partial correlations [r values] between brain volumes and internal jugular vein cross-sectional area by location, adjusted for cardiovascular risk factors.

		C7/T1			C5/C6			C4			C2/C3		
		LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total
NWBV	Males	*-.400 **	-.226	*-.346 **	-.292	-.261	*-.312 **	*-.343 **	-.237	*-.362 **	-.479 * *	-.163	*-.385 **
	Females	*-.226 **	-.287 **	-.301 **	-.145	*-.215 **	*-.209 **	.031	-.027	.000	.000	-.039	-.030
NGMV	Males	*-.338 **	-.222	-.313 *	-.274	-.272	-.310	*-.372 **	-.250	*-.388 **	-.427 * *	-.208	*-.390 **
	Females	*-.238 **	-.267 **	-.293 **	-.171	-.256 **	-.248 **	-.015	-.083	-.064	-.025	-.048	-.051
NWMV	Males	-.298	-.128	-.231	-.182	-.127	-.172	-.149	-.113	-.164	*-.328 **	-.029	-.203
	Females	-.117	*-.195**	-.187	-.050	-.070	-.069	.081	.060	.087	.034	-.011	.011
NLVV	Males	.478 **	.238	*.392 **	.450 **	*.323 **	.431 **	*.338 **	.156	.303	*.399 **	.264	.416 * *
	Females	.397 ***	*.196 **	.320 ***	*.242 **	.162	*.226 **	.112	.039	.091	.166	.010	.101
NCV	Males	-.310	-.206	-.289	-.246	-.230	-.269	*-.333 **	-.242	*-.360 **	-.431 * *	-.221	-.402 * *
	Females	*-.226 **	*-.245 **	-.273 **	-.150	-.249 **	*-.233 **	.003	-.082	-.053	-.007	-.039	-.033

Legend: NWBV-normalized whole brain volume; NGMV-normalized gray matter volume; NLVV-normalized lateral ventricle volume; NCV-normalized cortical volume.

Values reported are r values calculated using partial correlation analyses. Covariates include cardiovascular risk factors.

*** p<0.001; ** p<0.01; * p<0.05. Values less than 0.01 were considered significant (**bold**), and less than 0.05 were considered trends *(italics)*.

Table 3. Partial correlations [r values] between brain volumes and internal jugular vein cross-sectional area by location, adjusted for cardiovascular risk factors and age.

		C7/T1			C5/C6			C4			C2/C3		
		LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total
NWBV	Males	-.128	.088	-.001	-.037	.150	.075	-.089	.101	.021	-.264	*.384* *	.136
	Females	-.173	*-.203* *	*-.220* *	-.114	-.134	-.142	.053	.038	.056	-.047	-.073	-.082
NGMV	Males	.028	.163	.131	.041	.227	.167	-.087	.156	.063	-.145	**.435** **	.262
	Females	*-.196* *	-.169	*-.208* *	-.159	*-.193**	*-.203* *	-.008	-.030	-.025	-.103	-.104	-.137
NWMV	Males	-.213	-.023	-.123	-.092	.009	-.045	-.049	.003	-.029	-.251	.157	-.045
	Females	-.084	-.153	-.143	-.029	-.029	-.033	.087	.083	.106	.022	-.017	-.001
NLVV	Males	.273	-.028	.118	.283	.003	.159	.115	-.166	-.053	.179	-.142	.007
	Females	**.372** ***	.132	**.268** **	*.225* *	.107	.184	.115	.009	.074	*.199* *	.020	.127
NCV	Males	.067	.183	.164	.081	.289	.229	-.030	.162	.104	-.156	*.398**	.224
	Females	-.177	-.136	-.177	-.125	-.181	-.178	.019	-.029	-.008	-.072	-.086	-.105

Legend: NWBV-normalized whole brain volume; NGMV-normalized gray matter volume; NLVV-normalized lateral ventricle volume; NCV-normalized cortical volume.

Values reported are r values calculated using partial correlation analyses. Covariates include cardiovascular risk factors and age.

*** p<0.001; ** p<0.01; * p<0.05. Values less than 0.01 were considered significant (**bold**), and less than 0.05 were considered trends *(italics)*.

Table 4. Significance [z values (p values)] of changes in the partial correlation r values when controlling for age.

			C7/T1			C5/C6			C4			C2/C3	
		LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total	LIJV	RIJV	Total
NWBV	Males	-1.62 (.105)	-1.74 (.082)	*-1.97 (.049)*	-1.44 (.150)	*-2.29 (.022)*	*-2.18 (.029)*	-1.47 (.142)	-1.88 (.060)	*-2.19 (.029)*	-1.38 (.168)	-3.12 (.002)	-2.97 (.003)
	Females	-0.49 (.624)	-0.79 (.215)	-0.77 (0.441)	-0.28 (.780)	*-0.74 (.459)*	*-0.61 (.542)*	-0.2 (.842)	-0.58 (.562)	-0.50 (.617)	0.42 (.675)	0.30 (.764)	0.46 (.646)
NGMV	Males	*-2.08 (.019)*	*-2.14 (.032)*	*-2.50 (.012)*	-1.76 (.078)	-2.79 (.005)	-2.68 (.007)	-1.66 (.097)	*-2.26 (.024)*	-2.59 (.010)	-1.70 (.089)	-3.71 (<.001)	-3.72 (<.001)
	Females	-0.35 (.726)	-0.82 (.412)	-0.72 (.472)	-0.10 (.920)	-0.53 (.596)	-0.38 (.704)	-0.06 (.952)	-0.42 (.675)	-0.31 (.757)	0.62 (.535)	0.45 (.653)	0.69 (.490)
NLVV	Males	*-2.12 (.034)*	*-2.16 (.031)*	*-2.54 (.011)*	-1.82 (.069)	-2.91 (.004)	-2.79 (.005)	-.1.73 (.084)	*-2.25 (.024)*	-2.64 (.008)	-1.66 (.097)	-3.54 (<.001)	-3.58 (<.001)
	Females	-0.41 (.682)	-0.91 (.363)	-0.81 (.418)	-.0.20 (.842)	-.0.57 (.569)	-.0.46 (.646)	-0.13 (.897)	-0.42 (.675)	-0.36 (.719)	0.52 (.603)	0.38 (.704)	0.58 (.562)
NCV	Males	-1.62 (.105)	-1.74 (.082)	*-1.97 (.049)*	-1.44 (.150)	*-2.29 (.022)*	*-2.18 (.029)*	-1.47 (.142)	-1.88 (.060)	*-2.19 (.029)*	-1.38 (.168)	-3.12 (.002)	-2.97 (.003)
	Females	-0.49 (.624)	-0.79 (.215)	-0.77 (0.441)	-0.28 (.780)	*-0.74 (.459)*	*-0.61 (.542)*	-0.2 (.842)	-0.58 (.562)	-0.50 (.617)	0.42 (.675)	0.30 (.764)	0.46 (.646)

Legend: NWBV-normalized whole brain volume; NGMV-normalized gray matter volume; NLVV-normalized lateral ventricle volume; NCV-normalized cortical volume.

Values listed are z values and (p values) derived from applying Fisher's r-to-z transformation to the change in correlations presented in Tables 2 and 3. p values less than 0.01 were considered significant (**bold**), and less than 0.05 were considered trends *(italics)*.

Figure1. Examples of typical regions of interest (ROIs) relating to the internal jugular vein cross-sectional area at various neck levels (contoured in blue and indicated by the red arrows).