Sex differences in the rates and association of cerebral blood flow and glucose metabolism in normative ageing.

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Abstract

Although dysfunction in cerebral blood flow and glucose metabolism is linked to neurodegeneration, it is currently unclear if there are sex and age differences in their rates and association. Seventeen younger males (mean age 27.5 years), 20 younger females (28.4), 22 older males (76.6) and 20 older females (75.3) completed a MR/PET scan and cognitive battery. Females had higher CBF and CMR_{GLC} than males, regardless of age. CBF was lower in ageing. As CMR_{GLC} increased, the positive effect of higher CBF on working memory, cognitive flexibility, and processing speed also increased. Individuals with the highest CBF had the highest CMR_{GLC}. However, this association was moderated by sex and age, with significant negative associations across older females, possibly reflecting a compensatory response to a loss of blood flow and metabolism. We conclude that there are sex differences in the rates and association of cerebral blood flow and glucose metabolism in normative ageing and that high rates of blood flow and metabolism combine to support cognition.

Introduction

The risk of cognitive decline and neurodegeneration increases in older age[1]. Although a range of risk factors have been identified, metabolic and vascular factors are considered to be primary drivers of age-related cognitive decline[2,3]. For older women, their heightened risk of neurodegeneration is also related to hormonal changes, particularly the decline in estrogen levels that occurs during menopause[4]. Furthermore, declines in testosterone with ageing, a hormone mostly studied in men but also present in women in lower concentrations, is associated with an increased risk of dementia[5-7].

The heightened energy requirement of activated neurons regulates increases in cerebral blood flow (CBF) to the active area, a process known as functional hyperaemia or neurovascular coupling[8,9]. Cerebral blood flow and glucose metabolism are also tightly coupled within individuals to meet the energetic needs of the brain[10-13]. During brain activation it is well established that CBF, cerebral metabolic rates of glucose (CMR_{GLC}) and oxygen ($CMRO_2$) increase[11,14-16]. Correlated increases have been reported between CBF and CMR_{GLC} across multiple regions within the same animals, suggesting that separate regions are perfused more or less in proportion to their metabolic demands[17].

Factors that support or interrupt the supply of blood and metabolic substrates to the brain can alter the risk and progression of cognitive decline. For example, ageing is associated with reductions in CBF, CMR_{GLC}[18,19] and neurovascular coupling (see[20] for review). Sex differences in cerebral metabolism have also been reported in normative ageing. For example, females maintain higher rates of CBF than males across much of the adult lifespan, even into older adulthood[21-25], although sex differences in CBF may be diminished in late life[26,27]. Neurovascular coupling is similar in younger females and males[28] but reduces in older females[29].

Sex differences in CMR_{GLC} have primarily been studied in healthy younger and middle aged adults and the findings are equivocal[30-38]. In healthy older adults, males have higher glucose metabolism in the right insula, middle temporal gyrus, and medial frontal lobe, whereas females have higher metabolism in the hypothalamus[38]. In older individuals with dementia, higher metabolic rates together with a faster decline in metabolism have been reported in females than males[39-41], although the extent to which those results generalise to normative ageing is unclear.

Across-subject correlations of CBF and CMR_{GLC} are likely to be related to neurovascular coupling and reflect the consistency of the relationship among different individuals. Some studies have reported significant positive associations between CBF and $CMRO_2$ across individuals at rest and smaller positive correlations between CBF and CMR_{GLC}[42-44]. We recently showed that age and metabolic health status can moderate the association between CBF and CMR_{GLC} across individuals at rest[18]. These associations likely reflect that, even when the brain is not actively processing information, it maintains a baseline level of metabolic activity[45] that varies across individuals. Importantly, the largest proportion of the brain's energy budget is used to support spontaneous brain activity[46]. Therefore, a better understanding how the association between resting CBF and CMR_{GLC} change in normative ageing can deepen our understanding of brain metabolism and potentially aid in early diagnosis and treatment strategies.

Studying the brain as a functional network provides a useful framework for examining how neural information processing relates to cognition and behaviour[47]. Functional brain networks, such as the default mode, control, and attentional networks, play a fundamental role in cognition, as they connect specific regions involved in complex cognitive tasks, including attention, memory, decision-making, emotional regulation and motor control[48,49]. Disturbances in these networks in ageing or from metabolic dysfunction can lead to cognitive decline[50,51].

Here we investigated sex and age differences in the rates and association of CBF and CMR_{GLC} and cognition. Given the vascular and metabolic changes that occur in older adults and the hormonal changes that occur in females post-menopause[52,53], we hypothesise that females will have higher CBF and CMR_{GLC} than males and that these sex differences will be greater in younger than older adults. Given that neurovascular coupling is similar in younger females and males[28] but declines in older females[29], we also hypothesise that the association between CBF and CMR_{GLC} across individuals will be stronger in younger than older adults and in males than females. Finally, we hypothesise that lower CBF and CMR_{GLC} in functional networks will be associated with worse cognitive performance and processing speed.

Results

Demographic Factors and Cognition

All participants reported alignment between sex assigned at birth and gender identity. Significant sex or age group differences were found for all demographic variables, except for diastolic blood pressure and BMI (Table 1). However, none of the sex and age group interaction effects were significant at p-FDR < .05. All females in the older group reported being post-menopausal. Males had higher insulin, HOMA-IR and HOMA-IR2 than females. Older adults had fewer years of education than younger adults. Older adults also had higher fasting blood glucose and systolic blood pressure and lower cortical thickness. Given the impact of these demographic variables on brain metabolism, we repeated the analyses controlled for cortical thickness, blood pressure, resting heart rate, insulin resistance and BMI.

Older adults had lower HVLT discrimination index, fewer correct trials and seconds per correct count in the digit substitution task and slower reaction times in the stop signal task.

Sex and Age Differences in Whole Brain and Regional CBF and CMR_{GLC}

The mean and distribution of whole brain CBF and CMR_{GLC} for the whole sample and the sex and age groups are shown in Figure 1. The mean and standard deviation of regional CBF and CMR_{GLC} for the younger and older females and males are provided in the Supplement (Supplementary Tables 1 and 2).

Grey and white matter CBF in the whole sample had a normal distribution (.33 and .49) and kurtosis (-.07 and .41). Females had significantly higher whole brain grey and white matter CBF than males. Females also had higher CBF than males in 100 regions (see Figure 1D.1 and Supplementary Table 3). None of the regional sex differences in CMR_{GLC} survived correction for multiple comparisons (Supplementary Table 4).

Younger age was associated with significantly higher whole brain grey and white matter CBF and CMR_{GLC}. Younger adults also had higher grey matter CBF than older adults in 97 regions (Figure 1D.ii) and had higher glucose metabolism in 84 regions (Figure 1D.iii). The distribution of CMR_{GLC} in the whole sample was positively skewed (1.9) and leptokurtic (6.5). The positive skewness was largely due to one younger and one older female having CMR_{GLC} values above 6 ml/100g/min. We repeated the analyses excluding those participants. The age difference remained significant ($F(1,72) = 21.4$, $p < .001$). Given this result and the normative physiological values of the two participants[17,54], we retained them in the remaining analyses.

Controlling Demographic Variables: Sex and age differences in whole brain grey matter CBF were retained after adjusting for the demographic variables (see Supplementary Table 3). For white matter CBF, the significant sex difference but not the age group difference was retained when controlling for the demographic variables. Sex differences in CBF were also retained in 98 regions after adjusting for the demographic variables (Supplementary Table 5).

Only the age differences in CBF in the orbital frontal cortex remained significant when controlling for the demographic variables (Supplementary Table 6). None of the age differences in CMR_{GLC} at the whole brain or regional level remained significant (Supplementary

Table 7). However, the effect of cortical thickness on CMR_{GLC} was significant at the whole brain level and in 26 regions.

Sex and Age Differences in Network Level CBF and CMR_{GLC}

Statistically significant differences in sex and age group were found for CBF for all networks (Figure 2 and Supplementary Table 8). Older males had 12% to 29% lower CBF across networks than younger males; and older females had 19% to 26% lower CBF across networks than younger females. Older females also showed 16% to 25% higher average CBF than older males across the networks, and younger females showed 25% to 29% higher average CBF than younger males.

Significant age differences were also found for CMR_{GLC}, in all networks. Older males, on average, had 15% to 28% lower CMR_{GLC} across networks than younger males; and older females, on average, had 5% to 16% lower CMR_{GLC} across networks than younger females. Older females also had 13% to 18% higher CMR_{GLC} than older males; and younger females had 2% to 6% higher CMR_{GLC} than younger males. None of the sex and age group interaction effects were significant for network CBF and CMR_{GLC}.

Controlling Demographic Variables: Significantly higher CBF was found in females than males in all networks after adjusting for the demographic variables (Supplementary Table 9). The age differences in CBF in the limbic network was significant after adjusting for the demographic variables. No age differences in network CMR_{GLC} were significant after adjusting for the demographic variables, but cortical thickness significantly associated with CMR_{GLC} in all networks except the limbic and visual networks.

The Association of Whole Brain CBF and CMR_{GLC} Across Individuals

Whole Sample: Scatterplots of the grey and white matter associations of CBF with CMR_{GLC} are shown in Figure 3. There was a positive correlation across participants for both grey and white matter CBF and $CMR_{GLC.}$ The correlation for grey matter approached significance ($p = .077$). When the other demographic variables were controlled, there was a negative correlation for both grey and white matter CBF and CMR_{GLC} (Figure 3C and 3D). The correlation for grey matter CBF and CMR_{GLC} was significant ($p = .028$) and the correlation for white matter CBF and CMR_{GLC} approached significance ($p = .098$).

Sex and Age Group Differences: In the sex and age group analyses, none of the correlations were significant between whole brain grey and white matter CBF and CMR_{GLC} when no covariates were included (Figure 4A and 4B). Across younger females, a moderate positive correlation was found between grey and white matter CBF and CMR_{GLC}. The pattern was inverted for older females, who showed moderate negative correlations.. Across both younger and older males, small negative correlations were found for grey matter CBF and CMR_{GL} and the correlations were close to zero for white matter CBF and CMR_{GLC}.

When the other demographic variables were controlled, the negative correlations between grey and white matter CBF and CMR_{GLC} across older females were significant (Figure 4D). The correlations among older females also remained significant for grey matter and CMR_{GLC} ($r = -.625$, $p = .004$) and white matter and CMR_{GLC} ($r = -.624$, $p = .004$) when the two participants with CMR_{GLC} above 6 ml/100g/min were excluded.

The Association of Network CBF and CMR_{GLC} Across Individuals

Whole Sample: With the exception of the visual network, there was a positive correlation across participants between network CBF and CMR_{GLC} (Figure 5A.i and Supplementary Table 10). The largest correlations were in the control ($r = .19$), limbic (.21) and salience ventral attention (.24) networks. The correlation for the salience ventral attention network was significant at $p < .05$ but did not survive FDR-correction. When the other demographic variables were controlled, there was a negative correlation across all participants between network CBF and CMR_{GLC} (Figure 5B.i). The largest correlations were in the default ($r = -.13$), somatomotor (-.13), visual (-.14) and temporal parietal (-.21) networks.

Sex and Age Group Differences: Across younger females, small-to-moderate positive correlations were found between CBF and CMR_{GLC} in all networks (Figure 5A.iv). Across both younger and older males, small-to-moderate but non-significant negative correlations were found (Figure 5A.ii and 5A.iii). The pattern seen in younger females was inverted for older females, who demonstrated moderate-to-high negative correlations between network CBF and CMR_{GLC} (Figure 5A.v). When other demographic variables were controlled, the negative correlations across older females were significant for all networks except the limbic and control networks (Figure 5B.v). Significant differences were also found between the correlation of older males versus older females in all networks except the limbic and control networks; and between younger females and older females in all networks.

Network CBF, CMR_{GLC} and Cognition

The regression analysis of the CBF and CMR_{GLC} product term was significant for the HVLT discrimination index, reaction time in the category switch task, and the number of correct responses and seconds per correct response in the digit substation task (Table 2). The relationship between CBF and CMR_{GLC} in the salience ventral attention and temporal parietal networks was associated with performance on the HVLT discrimination index, such that as CMR_{GLC} increased, the positive effect of higher CBF on working memory also increased. The relationship between CBF and CMR_{GLC} in the visual, salience ventral attention, limbic and control networks was associated with the number of correct responses in the digit substitution task. Processing speed was also associated with the CBF and CMR_{GLC} relationship. In particular, the relationship between CBF and CMR_{GLC} in the limbic network was associated with reaction time in both the category switch task and seconds per correct response in the digit substitution task. The CBF and CMR_{GLC} relationship in the salience ventral attention and temporal parietal networks was also associated with reaction time in the category switch task, and in the control network was associated with seconds per correct in the digit substitution task.

The regression analysis of the CBF and CMR_{GLC} relationship controlling for the other demographic variables was significant for episodic memory, such that as CMR_{GLC} increased, the positive effect of higher CBF on episodic memory increased. The relationship between CBF and CMR_{GLC} in the salience ventral attention and temporal parietal networks was associated with performance in the HVLT discrimination index.

Discussion

In this study we found sex differences in the rates and association of cerebral blood flow and glucose metabolism in normative ageing. Older age was associated with hypoperfusion (reduced CBF) and hypometabolism (reduced CMR_{GLC}) across the brain in both females and males. However, females had significantly higher CBF than their male counterparts in both age groups. The reduction in the rate of glucose metabolism for older females was also lower than the reduction seen in males. We also found a striking negative association between CBF and CMR_{GLC} across older females that was not evident across older males or younger males and younger females. We also found significant associations between network CBF and CMR_{GLC} and cognition. As CMR_{GLC} increased, the positive effect of higher CBF on working memory, cognitive flexibility, and processing speed also increased.

Sex and Age Differences in CBF and CMR_{GLC}

Consistent with our hypothesis, younger females had higher whole brain, regional and network CBF than younger males. This CBF advantage was also seen in the older age groups, with older females having higher CBF than older males across the networks. The largest regional sex and age group differences in CBF were observed in frontal and temporal regions. Our results are concordant with previous studies showing that sex differences in CBF are evident across the adult lifespan[21,22,55], particularly in the frontal and temporal regions[23,56,57]. Our results are also consistent with the “last in first out” hypothesis of ageing which proposes that

brain functions and structures that develop later, such as the frontal regions of the brain, are more vulnerable to declines with ageing[58,59].

Older age was associated with lower CMR_{GLC} across the brain and the association was moderated by lower cortical thickness in older adults. These results are consistent with our previous reports[19] and other studies of ageing[38]. However, we did not find significant sex differences in CMR_{GLC}. There has been limited research on sex differences in CMR_{GLC} in healthy older adults. In contrast to our results, Yoshizawa et al.[37] reported some regional sex differences in glucose metabolism in adults aged over 60 years. The reason for these differences is unclear, although we note that Yoshizawa et al. did not undertake partial volume correction, which can impact measurement of CMR_{GLC}, particularly for older subjects[60,61].

The findings from previous studies of sex differences in CMR_{GLC} in younger adults have been equivocal[30-33,35-38,62,63]. One possible explanation is that researchers have not considered the phase of the menstrual cycle of female participants. In animals, glucose transporters in the brain[64] and cerebral metabolism[65] are sensitive to hormonal variation. In humans, hormone levels across the menstrual cycle modulate neural substrates, as indexed with fMRI[66]. Studies are needed to directly test whether CMR_{GLC} in humans varies across the menstrual cycle.

Age and sex differences in the association of CBF and CMR_{GLC} and Cognition

At the whole brain and network level, we found small-to-moderate positive correlations between CBF and CMR_{GLC} across participants. The correlation coefficients were similar to those reported in previous studies[40,43,67]. Our results suggest that, across the adult lifespan, individuals with the greatest amount of perfusion tend to have higher glucose metabolism. While the dynamics of resting state CBF and glucose metabolism differ from active states, our results also suggest that the principles of neurovascular coupling likely still apply[10,11], since the between-subject correlations at rest moderately reflect individual variations in baseline metabolism.

Our results contribute to the literature by revealing that other factors moderate the between-subject CBF and CMR_{GLC} association, including sex, age and physiological health. In terms of sex differences, younger males tended to show small-to-moderate negative correlations between CBF and CMR_{GLC}, whereas younger females tended to show small-to-moderate positive correlations. The direction of these associations was reversed in ageing, with the negative correlations particularly strong in older females.

Sex differences in human biology have been identified as a key contributor to different ageing trajectories and disease risks, including the risk for neurodegeneration. For example, changes in estrogen and testosterone contribute to the different courses of ageing in females and males (see[68] for review). Brain-derived hormones, as well as proteins and peptides that act in the brain, such as growth hormone, insulin receptor substrate 2 and insulin-like growth factor (IGF-1), also contribute to differences in brain ageing observed between the sexes[68]. Our results add to this research by suggesting that there are sex differences in the association of cerebral blood flow and glucose metabolism in ageing.

The significant negative association between CBF and CMR_{GLC} in older females was contrary to our stated hypothesis. We hypothesised a weakening of the association due to vascular and metabolic changes that occur in ageing and the post-menopausal hormonal changes in older females[69]. The negative CBF and CMR_{GLC} associations in older females reflect the maintenance of metabolic homeostasis within a relatively tight physiological range[18]. In other words, for older females to maintain the brain's supply of blood carrying oxygen and glucose, blood flow and glucose metabolic rates may increase in compensation for a decrease in the other and vice versa. Consistent with our stated hypothesis, we also found that the effect of network metabolism on cognition changed depending on the rate of both CBF and CMR_{GLC}, with a positive, significant association for visuospatial and episodic memory performance and processing speed. Together these results support the idea that the negative association of

CBF and CMR_{GLC} across older females might reflect a compensatory response in an effort to support cognition in the face of an age related loss of blood flow, glucose metabolism, or both.

To further understand the effects of age and sex on metabolism, we controlled for other physiological variables, including cortical thickness, blood pressure, resting heart rate, insulin resistance and BMI. With those variables as covariates, the number of brain regions showing age group differences in CBF was greatly reduced. The effect sizes suggest that each variable explains a small amount of shared variance of the influence of age on CBF. Interestingly, these physiological variables did not strongly influence the relationship between sex and CBF. However, they did change the direction of correlations between CBF and CMR_{GLC} across the whole sample from positive to negative and increased the strength of the negative correlation in older females. These results suggest that individual differences in CBF and CMR_{GLC} are significantly related to health markers, such as blood pressure, BMI and insulin resistance.

In this study all females in the younger group were pre-menopausal (we did not control for cycle phase or use of hormonal contraceptives). All females in the older group were post-menopausal and only three (15%) were on hormone replacement therapy (HRT). Therefore, it is tempting to conclude that the differences between young and older females are hormonal in origin. While we do not have data linking sex hormones to CBF in our sample, research suggests that sex hormones play a mediating role in the control of CBF. For example, CBF and carotid artery flow increase following acute estrogen administration and long-term hormone replacement therapy in post-menopausal women[70-72]. Future research could explore these linkages by measuring sex hormones together with cerebral blood flow and metabolism.

The reason that older males do not show a similar pattern of CBF and CMR_{GLC} associations to older females is unclear. It is possible that older males compensate for a reduction in blood flow and glucose availability through different mechanisms. Reductions in CBF in older men[7] have been attributed to the modulating role of testosterone in vascular function via angiogenesis and BBB permeability[5]. It is also possible that the small, positive correlation across older males is a relative “failure” of the negative coupling seen in healthy younger males and older females. Given that older males also have lower absolute rates of CBF and CMR_{GLC} than older females, it is possible that a failure of the coupling occurs when CBF, CMR_{GLC}, or both, drop below a critical threshold. This possibility could be tested in longitudinal studies that track the time course and trajectories of changes in the rates and coupling of CBF and CMR_{GLC}.

The study has a number of limitations, in particular the cross-sectional design which prevents conclusions about the causal relationship between age and cerebral blood flow and metabolism. As noted above, the differences found between groups may reflect unmeasured physiological, hormonal or health differences. Due to the relatively small sample sizes in the subgroup analyses, additional studies should be undertaken with larger samples. Research findings also suggest that CBF alterations across the lifespan may follow a non-linear patterns[73]. The absence of a “middle aged” adult cohort in the current study precluded non-linear relationships from being tested but should be a focus of future studies.

In conclusion, despite an age-related reduction in cerebral blood flow across the brain in both sexes, females have higher cerebral blood flow than their male counterparts regardless of age. There is a reduction of glucose metabolism in both sexes with ageing, although the loss is proportionally higher in males. Across the adult lifespan, individuals with the highest levels of cerebral blood flow tend to have the highest levels of glucose metabolism. However, other factors moderate this association, including sex, age and physiological health. Older females show a strong, negative association of blood flow and glucose metabolism across the brain, possibly reflecting a compensatory response to optimise cognition and available metabolic substrates. In males, the rates of blood flow and glucose metabolism are strongly attenuated in ageing and there is an absence of association. A better understanding of the interplay of sex hormones, cerebrovascular, and cerebral metabolic differences in females and males can

inform the development of interventions to optimise brain function and cognition across the adult lifespan.

Method

Ethical Considerations

The study protocol was reviewed and approved by the Monash University Human Research Ethics Committee. Administration of ionizing radiation was approved by the Monash Health Principal Medical Physicist, in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice (2005). For adult participants, an annual radiation exposure limit of 5 mSv applies. The effective dose in our study was 4.9 mSv. Participants provided informed consent to participate in the study.

Participants

Ninety participants were recruited from the general community via local advertising. An initial screening interview ensured that participants had the capacity to provide informed consent, and did not have a known diagnosis of diabetes, neurological or psychiatric illness, dementia. Participants were also screened for claustrophobia, non-MR compatible implants, and clinical or research PET scan in the past 12 months. Women were screened for current or suspected pregnancy. Participants received a $100 voucher for participating in the study.

Eleven participants were excluded from further analyses due to excessive head motion (n=2), incomplete PET or blood haemolysis (n=3), incomplete ASL scans (N = 2) or consistently high or low ASL or CMR_{GLC} values more than 2.5 standard deviations from the mean (N = 4). The final sample included 79 individuals, 17 younger males (mean 27.5; range 20-36 years), 20 younger females (28.4; 20-42), 22 older males (76.6; 66-84) and 20 older females (75.3; 66-89) (see Table 1).

Demographic and Cognitive Variables

Prior to the scan, participants completed an online demographic questionnaire including age, sex assigned at birth, gender identity, education, height and weight. Female participants reported if they were pre-, peri- or post-menopausal. Participants also completed a battery of cognitive tests of domains validated for use in ageing research[59] (see Supplement for details): delayed recall and a recognition discrimination from the Hopkins Verbal Learning Test (HVLT); longest correct series of forward and backward recall from a digit span test to index working memory; the proportion of correct trials and mean reaction time in a task switching test to index cognitive control; the probability of responding and reaction time in a stop signal task to measure response inhibition; and the number of correct responses and seconds per correct response in a digit substitution task to measure visuospatial performance and processing speed.

MR-PET Data Acquisition

Participants underwent a 90-minute simultaneous MR-PET scan in a Siemens (Erlangen) Biograph 3-Tesla molecular MR scanner. Prior to the scan, participants were requested to consume a high-protein/low-sugar diet for the 24 hours, fast for six hours and to drink 2–6 glasses of water. Participants were cannulated in the vein in each forearm and a 10ml baseline blood sample taken. At the beginning of the scan, half of the 260 MBq FDG tracer was administered via the left forearm as a bolus. The remaining 130 MBq of the FDG was infused at a rate of 36ml/hour over 50 minutes, minimising the amount of signal decay over the course of the data acquisition[74].

Participants were positioned supine in the scanner bore with their head in a 32-channel radiofrequency head coil. The scan sequence started with a non-functional MRI scans during the first 12 minutes, including a T1 3DMPRAGE (TA = 3.49 min, TR = 1,640ms, TE = 234ms, flip angle = 8°, field of view = 256 × 256 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3, 176 slices, sagittal acquisition) and T2 FLAIR (TA = 5.52 min, TR = 5,000ms, TE = 396ms, field of view = 250 × 250 mm^2, voxel size = .5 × .5 × 1 mm^3, 160 slices) to image the anatomical grey and white matter structures, respectively. Thirteen minutes into the scan, list-mode PET (voxel size = 2.3 x 2.3 x 5.0mm^3) and T2* EPI BOLD-fMRI (TA = 40 minutes; TR = 1,000ms, TE = 39ms, FOV = 210 mm^2, 2.4 × 2.4 × 2.4 mm^3 voxels, 64 slices, ascending axial acquisition) sequences were initiated. A 40-minute resting-state scan was undertaken in naturalistic viewing conditions watching a movie of a drone flying over the Hawaii Islands. At 53 minutes, a 5-delay pseudo-continuous arterial spin labelling (pcASL) scan was undertaken. Scan parameters were TR = 4,220 ms; TE = 45.46 ms; FOV = 240 mm; slice thickness = 3 mm; voxel size 2.5 x 2.5 x 3.0 mm^3. PLDs were 0.5, 1, 1.5, 2, and 2.5 s, duration of the labelling pulse was 1.51s.

Plasma radioactivity levels were measured throughout the scan. Beginning at 10-minutes post infusion, 5ml blood samples were taken from the right forearm using a vacutainer every 10-minutes, for a total of nine samples. The samples were directly placed in a Heraeus Megafuge 16 centrifuge (ThermoFisher Scientific, Osterode, Germany) and spun at 2,000 rpm (RCF ~ 515g) for 5 minutes. 1,000-µL plasma was pipetted, transferred to a counting tube, and placed in a well counter for four minutes. The count start time, total number of counts, and counts per minute were recorded.

Data Preparation and Preprocessing

Cortical Thickness For the structural T1 images, the brain was extracted in Freesurfer. The quality of the pial/white matter surface was manually checked, corrected and registered to MNI152 space using ANTs. Cortical thickness for the whole brain and the Schaefer 100 regions [75] was obtained from the Freesurfer reconstruction statistics[76].

Cerebral Blood Flow To quantify the ASL signal, the BASIL toolkit of the Oxford Centre for Functional MRI of the BRAIN (FMRIB)'s software library (FSL) was used (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BASIL). A calibration map M0 of proton density weighted image was acquired for each participant. Single−subject whole−brain CBF maps were calculated from perfusions weighted images, using direct subtraction of label and control volumes. Processing included motion correction, distortion correction with field map and partial volume correction. The model included a macro vascular component, adaptive spatial regularisation of perfusion, and incorporating T1 uncertainty. The arterial transit time was set at 1.3s, T1/T1b at 1.3/1.66s, and inversion efficiency at 0.85. The resulting CBF images in native space were aligned to the anatomical T1 images and normalised to MNI152 space with Advanced Normalization Tools (ANTs). Whole brain CBF grey matter and white matter and grey matter CBF for the Schaefer 100 regions were obtained for each participant.

PET Image Reconstruction and Pre-Processing The list-mode PET data were binned into 344 3D sinogram frames of 16s intervals. Attenuation was corrected via the pseudo-CT method for hybrid PET-MR scanners[77]. Ordinary Poisson-Ordered Subset Expectation Maximization algorithm (3 iterations, 21 subsets) with point spread function correction was used to reconstruct 3D volumes from the sinogram frames. The reconstructed DICOM slices were converted to NIFTI format with size 344 × 344 × 127 (size: 1.39 × 1.39 × 2.03 mm^3) for each volume. All 3D volumes were temporally concatenated to form a single 4D NIFTI volume. After concatenation, the PET volumes were motion corrected using FSL MCFLIRT[78], with the mean PET image used to mask the 4D data.

PET images were corrected for partial volume effects using the modified Müller-Gartner method in PetSurf[61]. We used a 25% grey matter threshold and surface-based spatial smoothing[60] with a Gaussian kernel with a full width at half maximum of 8mm.

Cerebral Metabolic Rates of Glucose Calculations of regional CMR_{GLC} were undertaken in Magia[79] using the FDG time activity curves for the Schaefer atlas regions. The FDG in the plasma samples was decay-corrected for the time between sampling and counting as the input function to Patlak models. Each participant's baseline plasma glucose (mmol) was also entered in the models.

Network-Level Measures In addition to the whole brain and regional measures, CBF and CMR_{GLC} were also calculated for the eight networks of the Schaefer atlas. The regions within the networks differ in cortical volume, hence, each regional value was weighted by the percentage its volume represented within the total network volume.

Statistical Analysis

All analyses were run in SPSS version 29.0 (https://www.ibm.com/products/spss-statistics).

Demographics and Cognition Univariate general linear models (GLMs) were used to test for sex, age group and sex x age group interaction effects for each demographic and cognitive measures. The main and interaction effects were FDR-corrected for multiple comparisons across the demographic and cognitive variables separately.

Because of the impact of demographic and other physiological factors on CBF and CMR_{GLC}[18], we repeated the analyses outlined below adjusting for years of education, cortical thickness, insulin resistance (HOMA-IR), blood pressure, heart rate and BMI.

Whole Brain Grey and White Matter CBF and CMR_{GLC} Separate GLMs were used to test for sex, age group and sex and age group differences in whole brain grey and white matter CBF and CMR_{GLC}. We also calculated the percentage difference in the mean CBF and CMR_{GLC} values between the groups.

Regional and Network Grey Matter CBF and CMR_{GLC} Separate series of GLMs was run to test for sex, age and sex and age group differences in grey matter CBF and CMR_{GLC} in the 100 regions and eight networks. Each series of GLMs was FDR-corrected at $p < .05$.

Association of Whole Brain and Network CBF and CMR_{GLC}. Whole brain and network level CBF and CMR_{GLC} associations across individuals were assessed in the whole sample and in the sex and age groups separately. Two series of correlations were undertaken. In the first, no covariates were included. For the second, the demographic variables were regressed on whole brain and network CBF and CMR_{GLC} separately across the whole sample. The residuals were then correlated across individuals in the whole sample and for the sex and age groups separately.

Association of Network CBF and CMR_{GLC} and Cognition To test the association between network CBF, CMR_{GLC} and cognitive performance, we ran separate multiple regression analyses using the 10 cognitive measures as the dependent variables. Stop signal reaction time, seconds per correct response in the digit substitution, category switch reaction time and the probability of reacting in the stop signal trials were multiplied by -1 so that higher scores reflect better performance. The cognitive scores were then converted to Z-scores. A product term of network CBF and CMR_{GLC} was calculated for each participant by multiplying their network CBF and CMR_{GLC} values. The product terms were used in the regression analyses to test whether the effect of CBF on cognition changes depending on the value of CMR_{GLC} and vice versa. The analyses were repeated using the product term of the residuals for CBF and CMR_{GLC} after regressing out the demographic variables.

Data and Code Availability Statement: The datasets and/or analysed used during the current study available from the corresponding author on reasonable request. No custom code was used.

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Tables

Table 1. Mean and standard deviation (SD) of demographics and cognitive test performance for the whole sample and the four groups based on sex and age category. p-values are for the sex, age group and sex and age group interaction effects from general linear models.

	Whole Sample (N = 79)		Younger Males (N = 17)		Younger Females (N = 20)		Older Males (N = 22)		Older Females (N = 20)		Sex Difference		Age Difference		Sex x Age Effect	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	p-FDR	p	p-FDR	p	p-FDR
Age (years)	53.5	24.9	27.5	5.4	28.4	7.0	76.6	5.4	75.3	6.8	NA	NA	NA	NA	NA	NA
Years of Education	16.9	3.2	17.9	2.7	17.9	2.7	16.9	2.8	15.1	3.8	0.197	0.297	0.009	0.023	0.538	0.924
Blood glucose (mmol/L)	5.0	0.5	4.9	0.3	4.7	0.4	5.3	0.5	5.0	0.6	0.032	0.080	0.002	0.007	0.584	0.924
Insulin (mU/L)	4.4	2.9	6.3	4.2	4.1	1.5	4.7	3.0	3.2	2.3	0.005	0.017	0.065	0.108	0.667	0.924
HOMA-IR	1.0	0.7	1.4	1.0	0.9	0.3	1.2	0.8	0.8	0.6	0.005	0.017	0.119	0.149	0.711	0.924
HOMA-IR2	0.6	0.4	0.8	0.5	0.5	0.2	0.6	0.4	0.4	0.3	0.005	0.017	0.345	0.345	0.924	0.924
Systolic BP (mmHg)	135.5	26.3	123.5	17.1	116.6	18.0	152.3	19.7	146.3	29.7	0.195	0.297	0.000	0.000	0.766	0.924
Diastolic BP (mmHg)	81.5	12.9	78.2	12.9	79.7	14.2	83.9	12.2	83.6	12.1	0.836	0.836	0.102	0.146	0.836	0.924
Heart Rate (BPM)	78.1	15.8	80.4	14.7	84.1	19.8	71.9	12.7	77.0	13.4	0.208	0.297	0.028	0.056	0.348	0.924
Body Mass Index (BMI)	25.0	4.1	24.3	3.0	24.4	5.8	26.3	2.5	24.7	4.3	0.415	0.519	0.237	0.263	0.482	0.924
Cortical Thickness (mm)	2.4	0.1	2.5	0.1	2.5	0.1	2.3	0.1	2.3	0.1	0.691	0.768	0.000	0.000	0.219	0.924
HVLT: Delayed Recall	8.3	2.6	9.2	3.0	9.3	2.0	6.5	2.3	8.7	2.0	0.034	0.340	0.002	0.005	0.057	0.190
HVLT: Rec. Discrimination	9.9	1.9	10.7	1.6	10.5	1.8	9.0	2.1	9.7	1.5	0.488	0.734	0.002	0.005	0.258	0.373
Digits Span: Forward	6.7	1.3	6.9	1.6	6.3	1.5	6.9	1.0	6.9	1.2	0.312	0.734	0.382	0.382	0.258	0.373
Digits Span: Backward	5.3	1.3	5.9	1.4	5.3	1.4	4.9	1.3	5.4	1.1	0.808	0.808	0.161	0.201	0.057	0.190
Cat Switch: % Correct Trial	91%	11%	96%	6%	92%	9%	88%	13%	90%	11%	0.546	0.734	0.052	0.074	0.298	0.373
Cat Switch: Mean RT (sec)	1.8	0.6	1.3	0.2	1.5	0.5	2.3	0.7	1.9	0.5	0.642	0.734	0.000	0.000	0.014	0.140
Digit Sub: Correct Count	44.4	22.4	65.3	9.0	62.7	14.2	28.5	11.4	26.7	16.9	0.473	0.734	0.000	0.000	0.888	0.948
Digit Sub: Secs Per Correct	5.3	13.6	1.9	0.2	2.0	0.4	5.1	2.5	4.9	3.8	0.244	0.734	0.031	0.052	0.262	0.373
Stop Signal: Prob Reacting	49.2	11.5	51.9	13.6	50.2	12.3	45.6	3.3	49.7	14.0	0.661	0.734	0.190	0.211	0.263	0.373
Stop Signal: RT (msec)	0.56	0.12	0.53	0.16	0.52	0.99	0.60	0.96	0.58	0.13	0.539	0.734	0.029	0.052	0.948	0.948

Three participants didn't answer the years of education question; baseline blood samples not available for three participants for insulin and HOMA-IR calculations. Three participants were more than three standard deviations above the mean for the Digit Substitution seconds per correct measure and were excluded from analyses of cognitive data.

Table 2. Regression analyses of network CBF, CMR_{GLC} and cognition. The standardised beta weights are for the product term of network CBF and CMR_{GLC} and indicate how the effect of network CBF on cognition changes as the level of network CMR_{GLC} changes, and vice versa. *p < .05; **p < .001.

	HVLT		Digit Span		Category Switch		Digit Substitution		Stop Signal	
	Delayed Recall	Discrim Index	Backward Span	Forward Span	% Correct	Reaction Time	Number Correct	Secs Per Correct	Probability of Reacting	Reaction Time
	No Covariates									
ANOVA F-value	1.6	2.1	1.4	1.0	0.6	5.4	8.7	4.0	0.4	1.6
ANOVA p-value	0.127	0.043	0.208	0.474	0.733	<.001	<.001	<.001	0.897	0.144
ANOVA p-FDR value	0.240	0.107	0.297	0.593	0.814	<.001	<.001	<.001	0.897	0.240
Variance Explained	16%	20%	14%	10%	7%	38%	50%	32%	5%	15%
Standardised Beta										
Visual	0.14	0.37	-0.17	-0.08	0.09	0.10	-0.59*	-0.57	0.13	0.17
Somatomotor	-0.35	-0.54	-0.90	-0.41	0.14	-0.01	-0.77	-0.46	-0.44	-0.77
Dorsal Attention	-0.09	-0.52	1.89	0.62	-0.79	-0.15	0.66	0.81	0.35	0.86
Salience Ventral Attention	1.97	2.04*	-0.71	-0.28	1.13	1.84*	2.03*	1.76	0.98	0.51
Limbic	0.59	0.30	0.20	0.66	0.55	1.31**	1.03**	0.88*	0.30	0.39
Control	-1.05	-0.64	-0.42	0.58	-0.75	-1.43	-1.80*	-2.60*	0.03	-0.93
Default	-0.13	0.67	0.10	-0.36	-0.12	0.43	0.87	0.78	-0.62	0.02
Temporal Parietal	-0.79	-1.49*	-0.22	-0.59	-0.07	-1.73*	-0.93*	-0.30	-0.62	0.05
	Controlling Years of Education, Cortical Thickness, HOMA-IR, Blood Pressure, Heart Rate and BMI									
ANOVA F-value	1.6	3.0	0.8	1.3	0.7	1.2	0.5	0.3	1.1	0.4
ANOVA p-value	0.151	0.007	0.595	0.255	0.659	0.311	0.869	0.958	0.358	0.941
Variance Explained	16%	27%	9%	14%	8%	13%	6%	4%	12%	4%
Standardised Beta										
Visual	-0.55	-0.25	-0.16	-0.14	0.29	0.05	-0.13	-0.12	-0.57	0.09
Somatomotor	0.47	0.13	0.90	0.79	-0.11	-0.24	-0.27	-0.22	0.82	0.30
Dorsal Attention	-0.83	-0.58	-0.69	-0.24	0.00	-0.26	0.00	0.12	-1.13	-0.47*
Salience Ventral Attention	-0.87	-1.18*	-0.64	-0.42	-0.64	0.23	0.35	0.09	-0.32	-0.35
Limbic	0.21	0.46	-0.03	-0.12	-0.02	-0.63*	0.07	0.04	0.22	0.20
Control	1.20*	0.65	0.92	1.09*	0.51	0.34	0.41	0.44	0.03	0.59
Default	-0.04	0.23	-0.59	-0.80	-0.48	0.02	-0.63	-0.28	0.88	-0.21
Temporal Parietal	0.57	0.86*	0.31	-0.29	0.37	0.45	0.35	-0.06	0.07	-0.19

Note: Stop signal reaction time, seconds per correct response in the digit substitution, category switch reaction time and the probability of reacting in the stop signal trials were first multiplied by -1 so that higher scores reflect better performance.

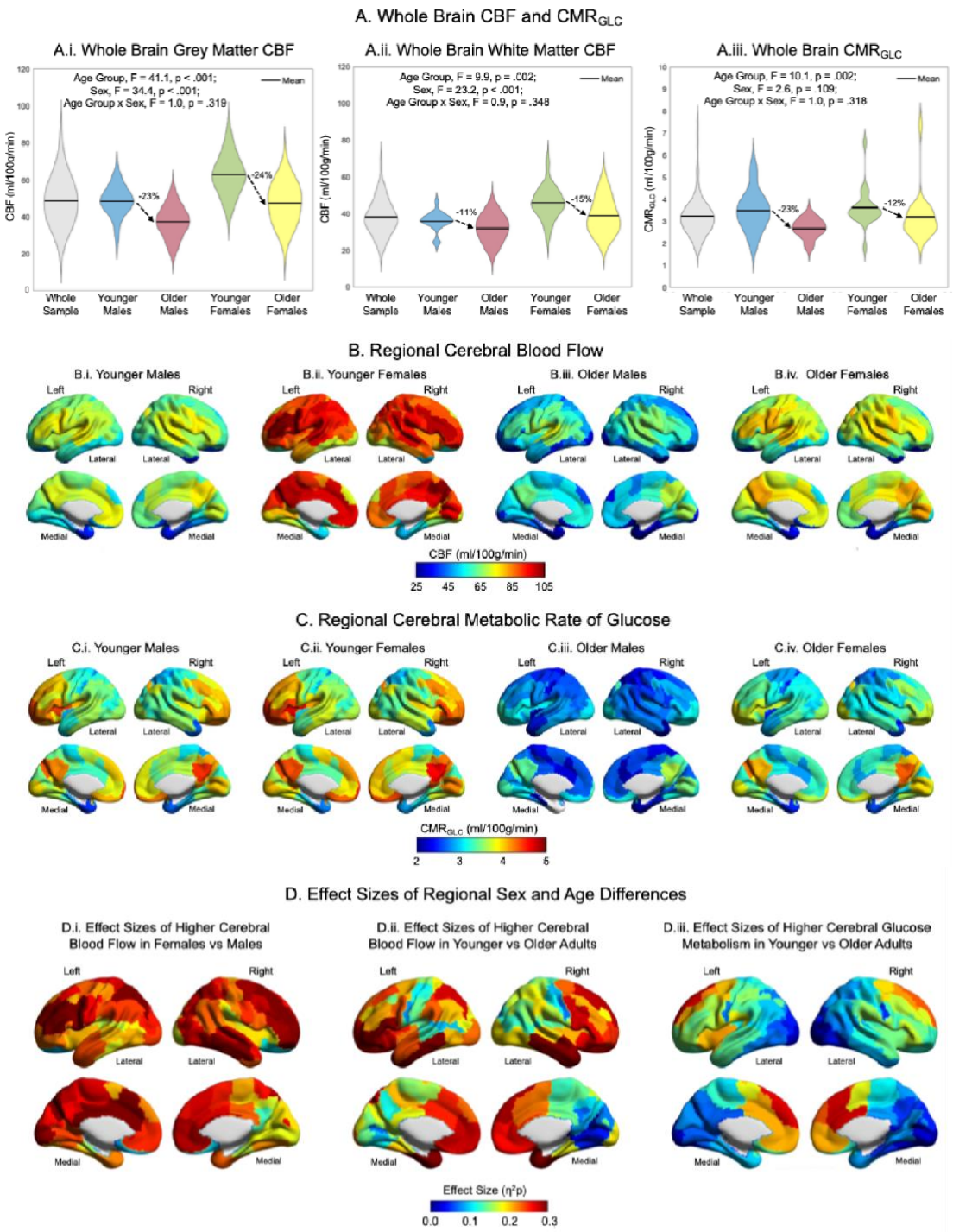

Figure 1. Sex and age group differences whole brain and regional CBF and CMR_{GLC}. Violin plots of whole brain grey and white matter cerebral blood flow and glucose metabolism (A). The dotted arrows and percentages show the decrease in the mean CBF and CMR_{GLC} of young and older males and females. Sex and age group mean regional CBF (B) and CMR_{GLC}. (C). Group differences in regional cerebral blood flow and glucose metabolism. Effect sizes for higher CBF in females than males; age group differences in CBF; and age group differences in CMR_{GLC} (D). All regions showed females > males and younger > older in CBF and CMR_{GLC}, hence hot (red/yellow) colours indicate larger effect sizes for females vs males and older versus younger, whereas cold (blue/teal) colours indicate smaller effect sizes closer to zero. None of the sex differences for CMR_{GLC} and sex and age group interaction effects were significant at p-FDR<.05 and hence are not shown. The GLMs testing for significant sex, age group and sex x age group interaction effects are presented in Supplementary Tables 8-9, and the analyses controlling for the demographic variables in Supplementary Tables 10-11.

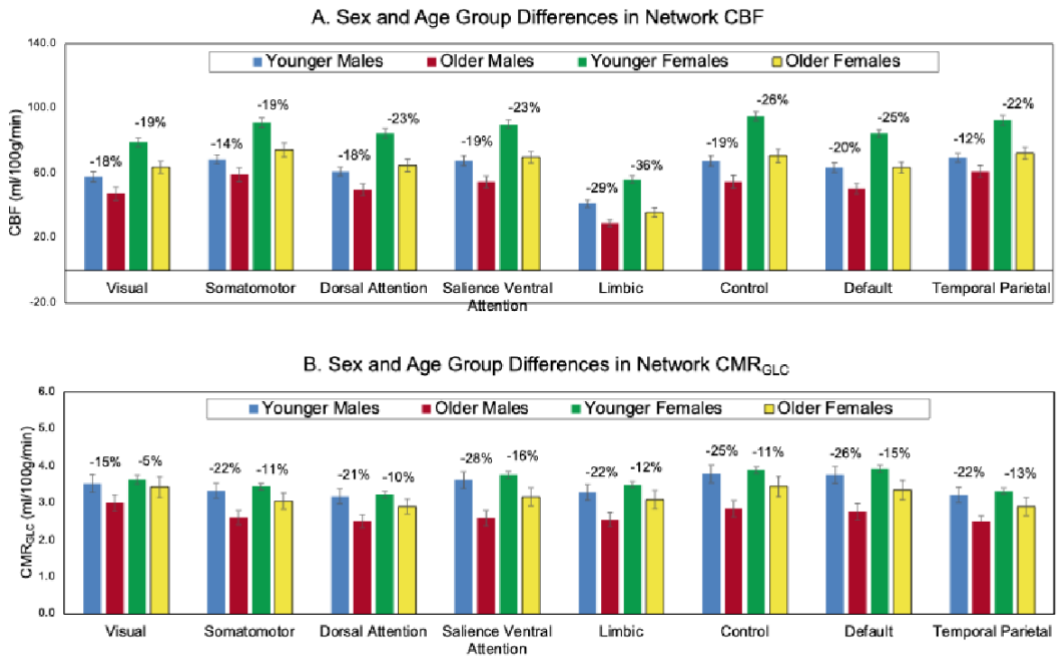

Figure 2. Sex and age group differences in the rates of network cerebral blood flow and glucose metabolism. Mean and standard errors (error bars) in the rates of (A) CBF and (B) CMR_{GLC} for younger and older males and females. Significant sex and age group differences were found for all networks for CBF and significant age group differences for CMR_{GLC} in all networks except the visual network (p-FDR < .05; see Supplementary Tables 2). The numbers above the bars show the average differences in CBF (A) and CMR_{GLC} (B) for younger and older males and younger and older females. When all of the demographic measures were included in the models, sex differences were retained for all networks for CBF, however, none of the age group differences were significant for either CBF or CMR_{GLC} (Supplementary Table 4). The age group effect on CMR_{GLC} was moderated by cortical thickness, which was significant for all networks except the visual and limbic networks.

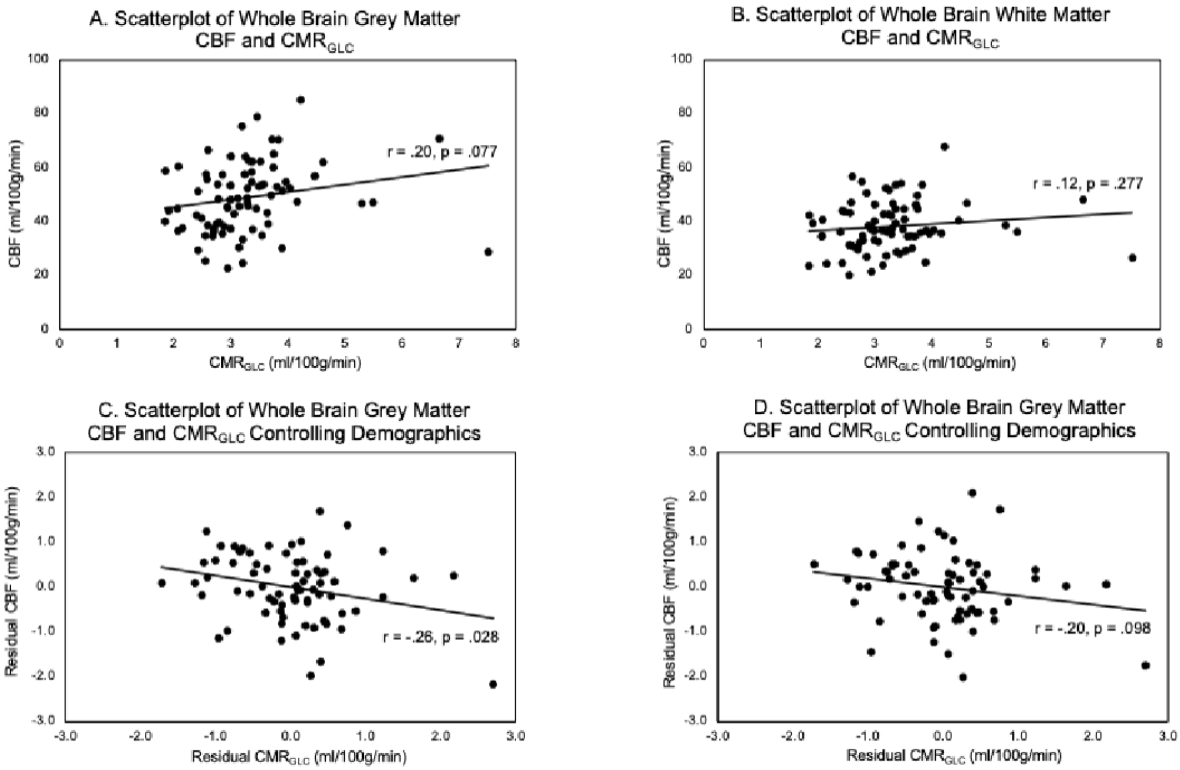

Figure 3. Scatterplots and correlations of whole brain cerebral blood flow and glucose metabolism in the whole sample. Scatterplots and correlations of whole brain grey matter CBF and CMR_{GLC} (A) and white matter CBF and CMR_{GLC} (B). Scatterplots and correlations of residuals of whole brain grey matter CBF and CMR_{GLC} (C) and white matter CBF and CMR_{GLC} (D), controlling for demographics. Whole brain cortical thickness, years of education and physiological variables (HOMA-IR, blood pressure, resting heart rate and BMI) were regressed on CBF and CMR_{GLC} and the residuals saved for each participant.

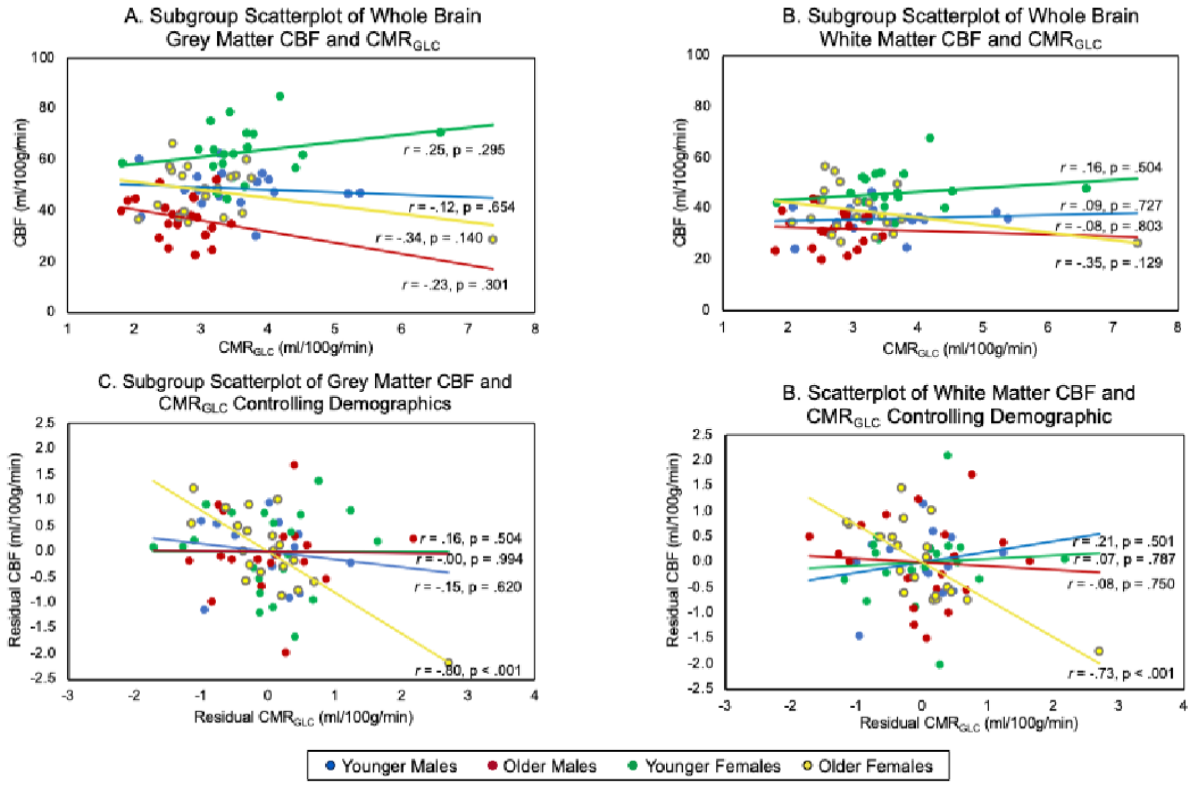

Figure 4. Scatterplots and correlations of whole brain cerebral blood flow and glucose metabolism in the sex and age subgroups. Scatterplots and correlations of whole brain grey matter CBF and CMR_{GLC} (A) and white matter CBF and CMR_{GLC} (B). Scatterplots and correlations of residuals of whole brain grey matter CBF and CMR_{GLC} (C) and white matter CBF and CMR_{GLC} (D), controlling for demographics. Whole brain cortical thickness, years of education and physiological variables (HOMA-IR, blood pressure, resting heart rate and BMI) were regressed on CBF and CMR_{GLC} across the whole sample and the residuals saved for each participant. The residuals were then correlated across participants within each subgroup.

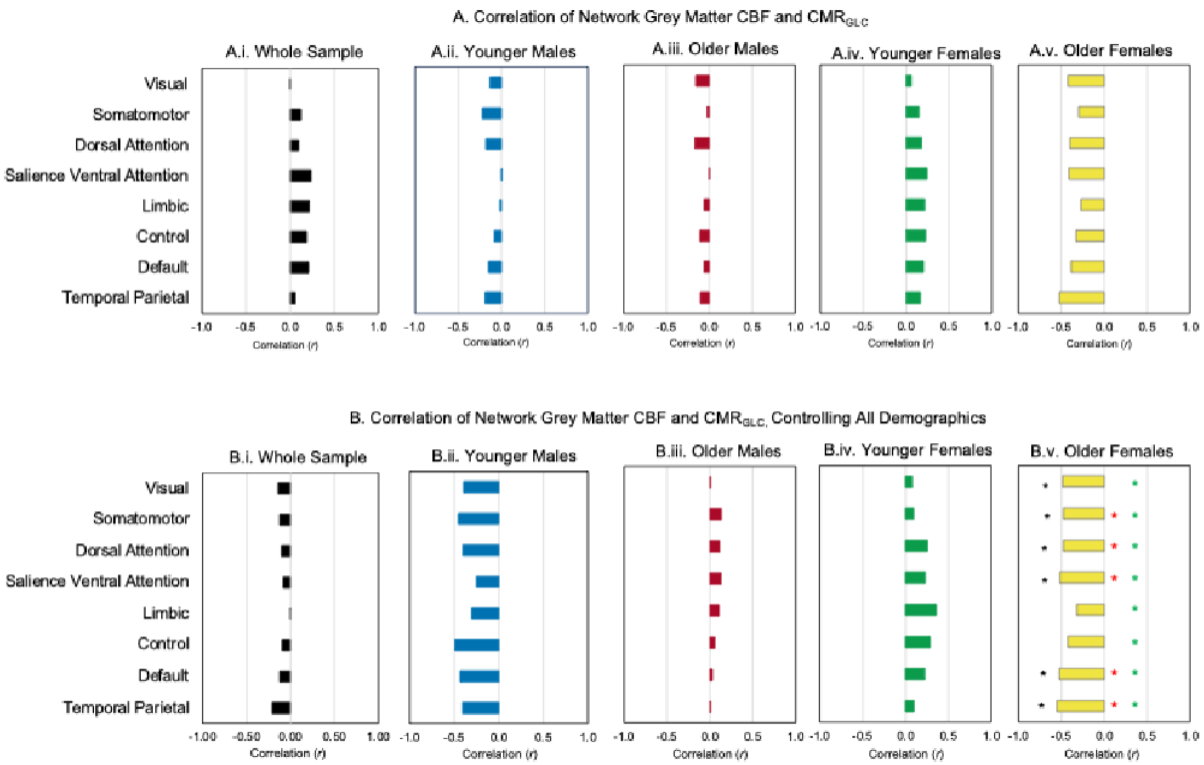

Figure 5. Association of network cerebral blood flow and glucose metabolism for the whole sample and the sex and age groups. Associations with no covariates (A) and controlling for all demographics (B). In (B), demographics were regressed out of CBF and CMR_{GLC} across the whole sample, before the correlations of CBF and CMR_{GLC} were calculated for each group. Black asterisk (*) to the left of the bars indicates a significant correlation different from zero at p-FDR < .05. Red and green asterisks indicate significant effects of sex and age: red asterisk (*) indicates significant difference in correlation between older males and older females at p-FDR < .05; and green asterisk (*) significant difference in correlation between younger females and older females at p-FDR < .05. Significant differences were also found between younger males and younger females for the dorsal attention, limbic, control and default networks controlling for all demographics at p-FDR < .05. The test of significant sub-group differences in correlations are also summarised in Supplementary Table 10.