Sex differences in cerebrovascular reactivity and cerebral blood flow across the lifespan

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PURPOSE

Investigating the time-course of cerebrovascular aging in both sexes across five decades of life

HYPOTHESIS

Cerebrovascular health will decline during the healthy aging process in males and females

KEY FINDINGS

CVR and CBF decline during aging in both sexes. Females have higher CBFs during their lifespan compared to men

Introduction

- Aging is associated with declines in cerebrovascular health, with some differences observed between males and females[1].
- Cerebral Blood Flow (**CBF)** declines linearly in both sexes[1].
- Cerebrovascular reactivity (**CVR**) has also been shown to decline with age [1,2,3,4], but sex effects are currently unclear.
- It is likely that some of the sex differences observed in CBF and CVR are due to differences in sex hormones across the lifespan in males and females , since sex hormones have been shown to influence vascular and endothelial properties[5].
- Given the different time course of cerebrovascular disease in both sexes, sex-specific analysis of the cerebrovascular health is crucial to understand the true impact of aging on cerebrovascular health.
- Here, we investigate the time-course of cerebrovascular aging in adult males and females across five decades of life.

Methods

- Data acquisition was completed as part of larger studies wherein 62 **females** and 34 **males** (mean age= 57.4±17.2) were included (Table 1 for more details on each study).
- MRI acquisitions were completed across three studies with three different 3T Siemen's scanners. A pseudo-continuous arterial spin labelling (**pCASL**) sequence was acquired in all participants at rest and during a hypercapnia manipulation, as well as a T1 sequence.
- Preprocessing of pCASL data included brain extraction and motion correction in FSL and MATLAB.
- Resting CBF was quantified using a cerebral spinal fluid (CSF) M0 mask using FSL.
- CVR maps of 5% CO2 inhalation during hypercapnia were estimated from the Blood-oxygenated label dependent signal (**BOLD**) image.
- CBF and CVR maps were registered to MNI space using ANTS.

Results

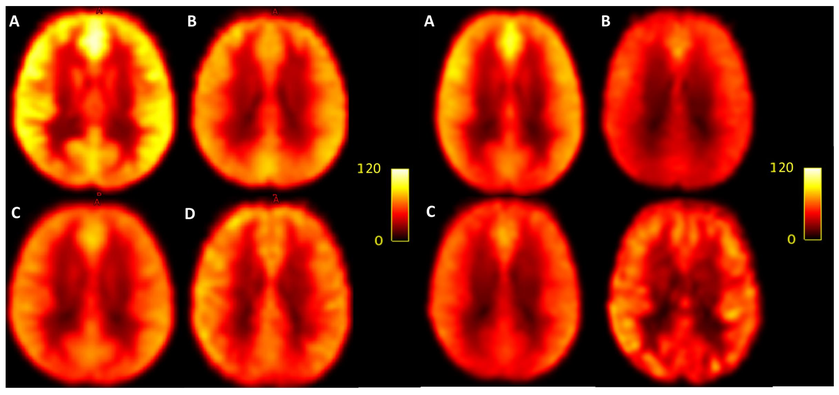

Figure 1: Mean CBF (ml/100g/min) for females: **A**- 20 to 29 yo (n=9); **B**- 50 to 59 yo (n=8); **C**- 60 to 69 yo (n=27); **D**- 70 to 79 yo (n=7);

Figure 2: Mean CBF (ml/100g/min) for males: **A**- 20 to 29 yo (n=14); **B**- 50 to 59 yo (n=6); **C**- 60 to 69 yo (n=9); **D**- 70 to 79 yo (n=4);

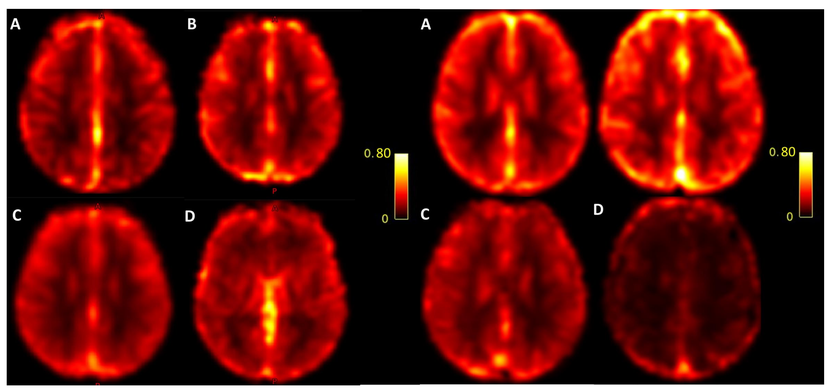

Figure 3: Mean CVR (%BOLD change/ΔmmHg CO2) for females: **A**- 20 to 29 yo (n=9); **B**- 50 to 59 yo (n=8); **C**- 60 to 69 yo (n=27); **D**- 70 to 79 yo (n=7);

Figure 4: Mean CVR (%BOLD change/ΔmmHg CO2) for males: **A**- 20 to 29 yo (n=14); **B**- 50 to 59 yo (n=5); **C**- 60 to 69 yo (n=9); **D**- 70 to 79 yo (n=4);

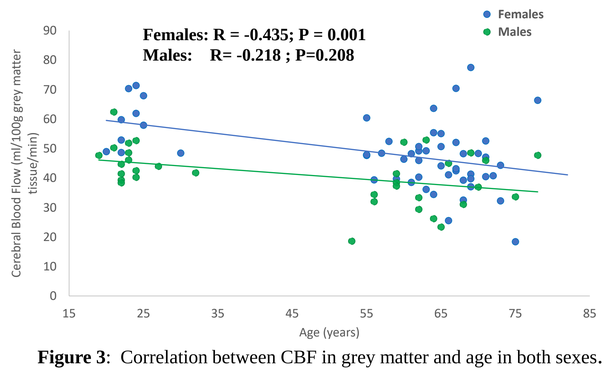

Figure 3: Correlation between CBF in grey matter and age in both sexes.

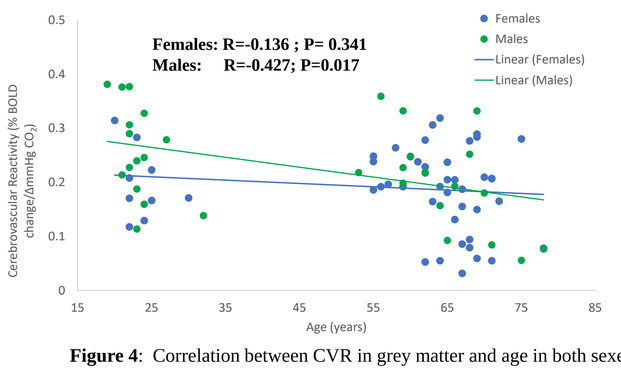

Figure 4: Correlation between CVR in grey matter and age in both sexes.

Table 1. Imaging Parameters

Sex / Decline rate	Females	Males
CBF decline	0.435 ml/100g/min per year	0.218 ml/100g/min per year
CVR decline	0.136 %BOLD change/ΔmmHg CO2 per year	0.427 %BOLD change/ΔmmHg CO2 per year

Table 2. CBF and CVR decline rates in grey matter in both sexes.

Study	Hypercapnia manipulation	Post Labeling Delay (PLD)	Labeling Duration	Repetition Time (TR)
1	2-2-2-2-2-2-2 min	1.8s	1.512s	4s
2	2-2-2-2-2 min	0.9s	1.6s	3s
3	2-2-2-2-2 min	1.55s	1.512s	4.15s

Discussion

- **CVR** and **CBF** demonstrated significant decline across the lifespan in both sexes.
- Females showed higher CBF than males across the lifespan.
- Male CVR decreases at significantly faster rate than female CVR.
- Counters previous work with TCD where females had higher CVR across lifespan[3], but is consistent with previous work using MRI where males (25-42 yo) demonstrated greater CVR[4] – potentially reflecting a difference in the underlying physiological component measured.
- Future studies should seek to further explore these sex differences by measuring sex hormones to investigate their role both cross-sectionally and longitudinally across the lifespan.
- Finally, these relationships should be investigated in a larger sample with an equal distribution of males and females.

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