Arterial Pulsatility, Cognitive Decline and Dementia

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NIH NIA

Disclosures

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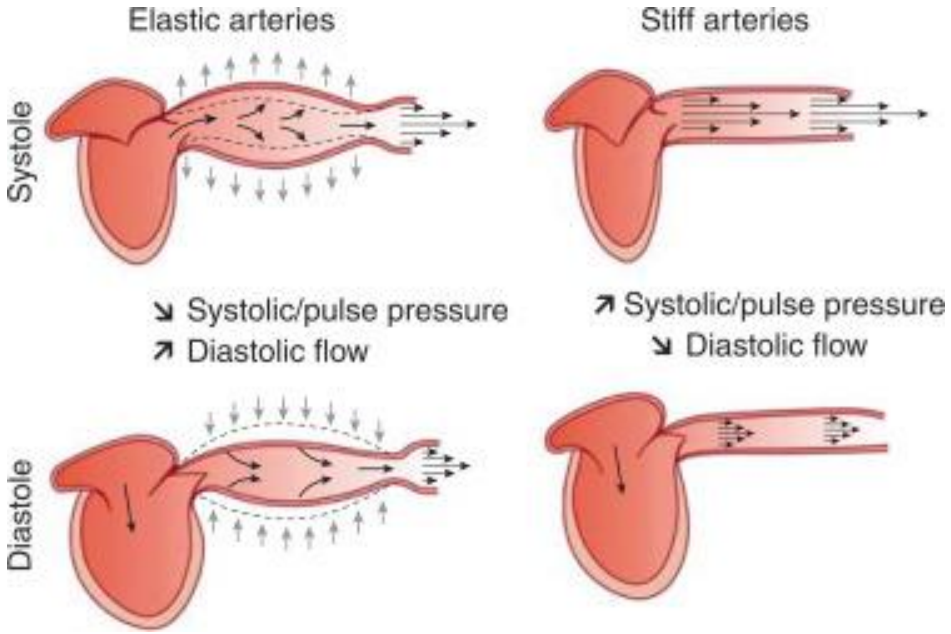
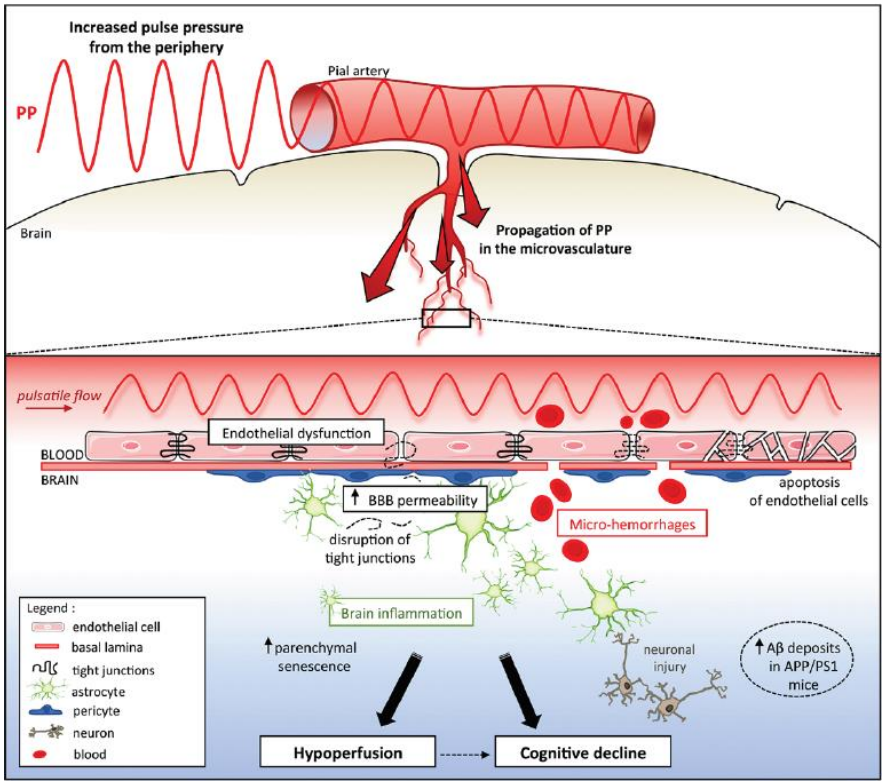
Ageing, Pulsatility, and the Brain

Predominant form of hypertension from mid-life is isolated systolic hypertension

Results from stiffening of major elastic arteries and subsequent increase in pulse pressure

Potential for end-organ damage, particularly in low resistance / high flow vascular beds such as kidney and brain





De Montgolfier et al 2019 Hypertension 73:217-228

Strength of Evidence

Human Studies

MRI changes / Cognitive Decline / Dementia related to:

Aortic Stiffness

Carotid Stiffness

Systolic / Pulse Pressures

Surrogate markers

-

Can we quantify the pulsatile energy that the brain may actually 'see'?

Animal Studies

Induced arterial stiffness / increased pulsatility (e.g. arterial ligation/carotid calcification/etc)

Increased inflammation

Increased ROS

Endothelial Dysfunction

BBB Dysfunction

Cell Apoptosis

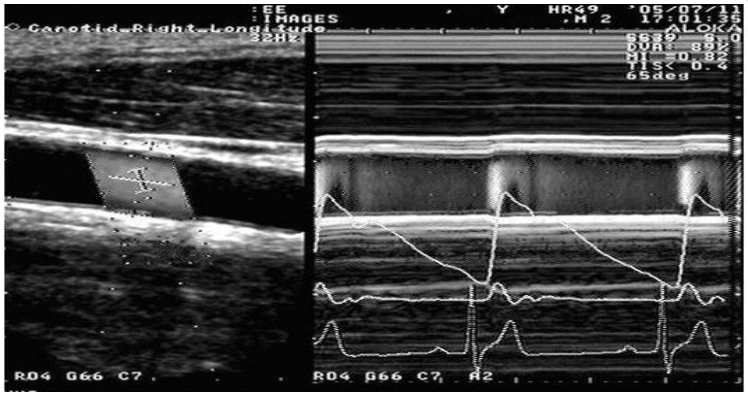
Microhaemorrhages

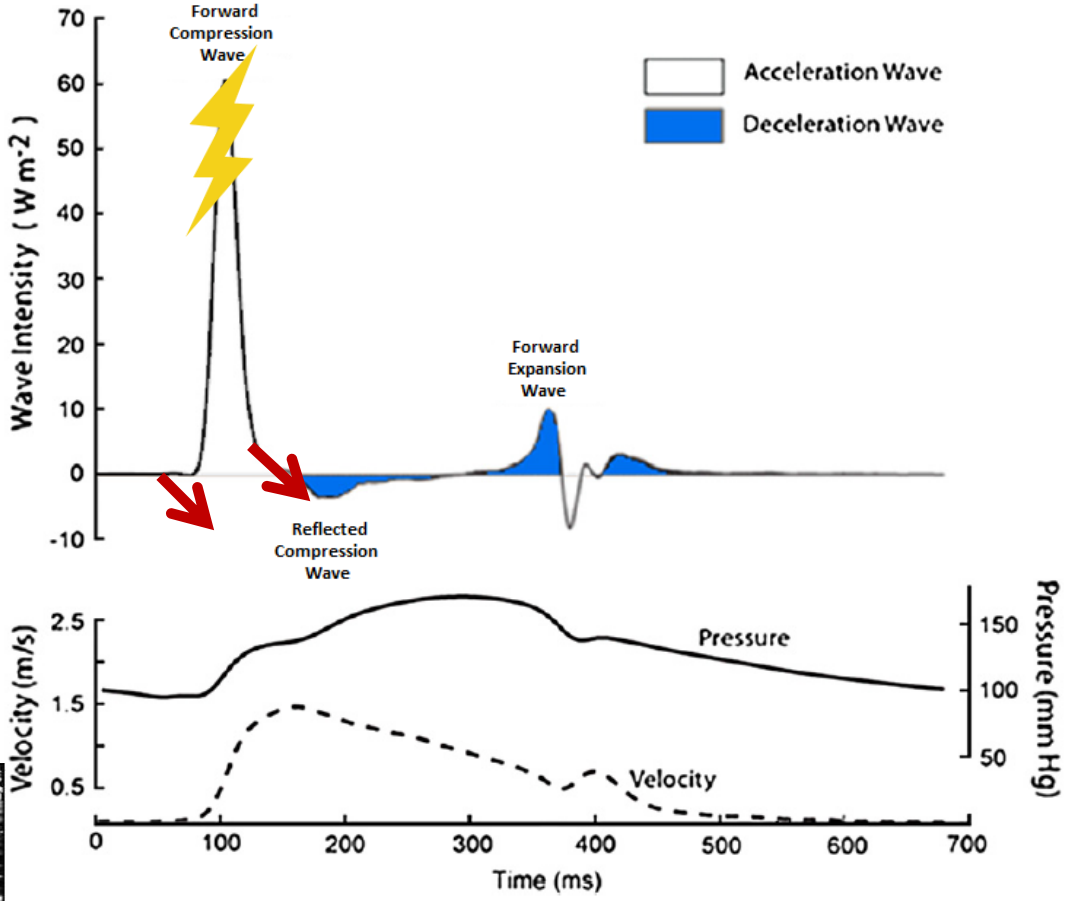
Carotid Wave Intensity Analysis

Performed non-invasively in the common carotid artery using duplex Doppler ultrasound

Simultaneous measures of vessel diameter and blood velocity used to calculate wave intensity

Allows energy transfer per unit area **and** direction of wave travel to be determined





WI = dP.dU (W/m^2)

or

WI = (dP/dt).(dU.dt) ($mmHg.m/s^{-3}$)

The Whitehall II Study

- Ongoing cohort study of persons originally employed by the British Civil Service
  - 10,308 persons aged 33-55 recruited at start of study between 1985-1988
- Extensive phenotyping over twelve phases of data collection since then – latest 2015-2016

1985-2016

Demographics

CV Risk Factors

Disease Outcomes

2002

Carotid Structure and Stiffness

Carotid Wave Intensity

Aortic Stiffness

2002-2016

Cognitive Function

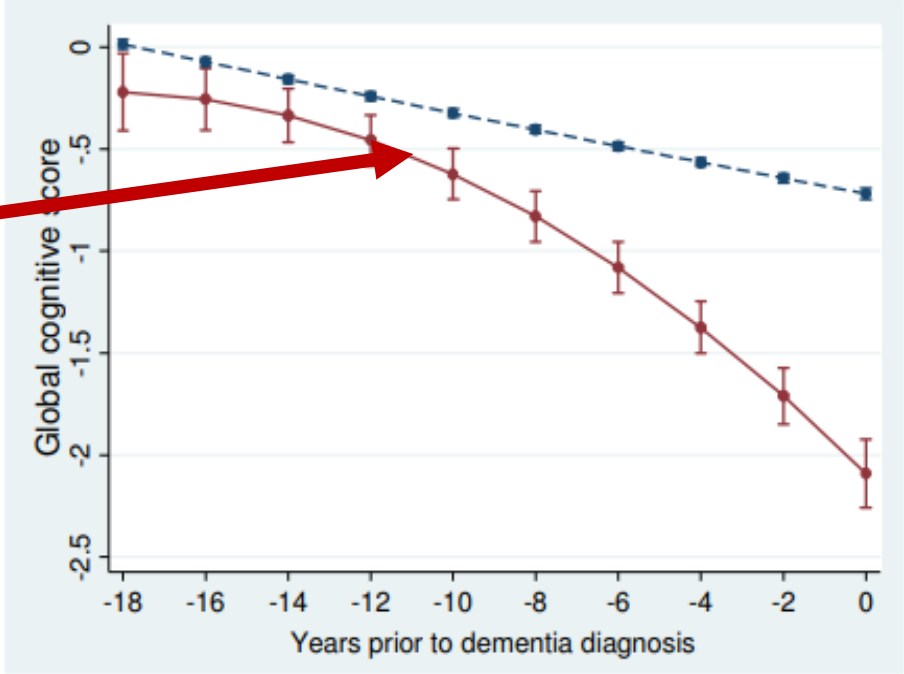
Dementia Diagnosis

Cerebral MRI

Cognitive Assessments

- Test battery administered in four phases (2002-2016).
- Comprising individual domains testing memory, executive function, and fluency (both semantic and phonemic).
- Global cognitive score created using individual domains and mixed linear models used to create trajectories of decline for each.

Progressive decrease in global cognitive score 10-12 years prior to dementia diagnosis



Sabia et al 2017 BMJ 357: j2079

Hypothesis

The transmission of high intensity pulsatile waves towards the cerebral circulation in mid- to late-life (~ 60 years of age) will be associated with accelerated cognitive decline in prospective follow-up (11-14 years)

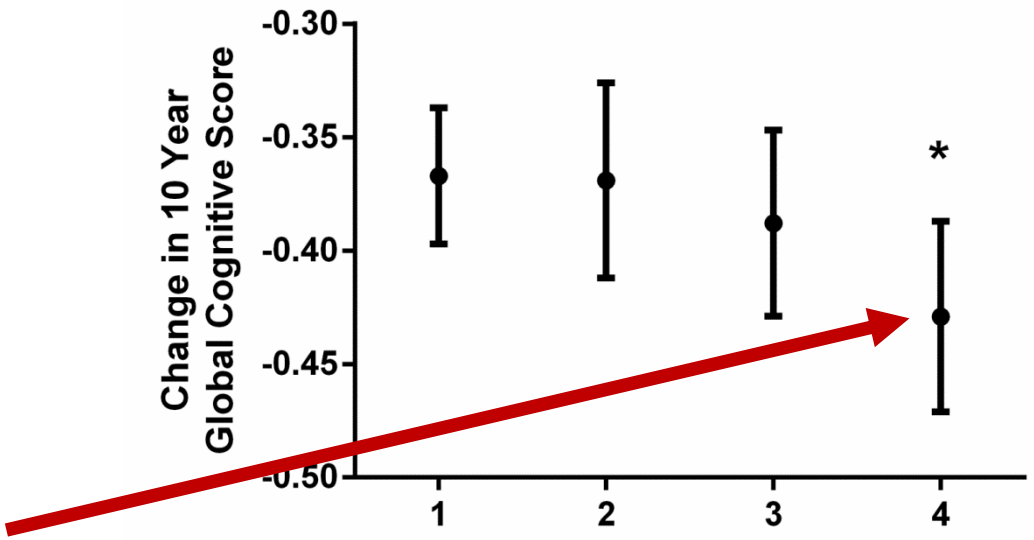
Baseline Characteristics

	[Mean (SD) or %]				p-value for heterogeneity
	Baseline carotid forward compression wave intensity quartile				
	Lowest Quartile (Q1)	Quartile 2	Quartile 3	Highest Quartile (Q4)	
Number	**781**	**813**	**811**	**786**	
Age, y	61.2 (5.8)	60.3 (5.6)	60.7 (5.8)	60.8 (5.9)	0.01
Female, %	39.1	26.2	18.3	17.1	<0.001
Ethnicity					0.07
- *White*	92.3	94.1	93.5	93.0	
- *Non-White*	7.7	5.9	6.5	7.0	
BMI (kg/m^2)					<0.001
- *Underweight (<20.0)*	4.4	3.6	2.2	2.2	
- *Normal weight (20.0 - 24.9)*	39.8	36.8	38.2	28.1	
- *Overweight (25.0 – 29.9)*	38.9	38.2	45.5	48.4	
- *Obese (≥ 30.0)*	16.9	28.1	14.1	21.4	
Wave Intensity (mmHg/m/s^3)	4795 (923)	7115 (582)	9401 (780)	14949 (4563)	<0.001
Blood Pressure (mmHg)					
- *Systolic Blood Pressure*	122.7 (12.9)	127.4 (13.8)	130.3 (13.4)	137.0 (14.2)	<0.001
- *Pulse Pressure*	44.9 (7.3)	49.5 (7.3)	52.7 (7.6)	58.4 (8.8)	<0.001
- *Diastolic Blood Pressure*	77.8 (8.6)	78.0 (9.2)	77.6 (8.8)	78.6 (8.9)	0.18
- *Mean Arterial Pressure*	92.8 (9.6)	94.5 (10.4)	95.2 (9.9)	98.0 (10.1)	<0.001
Education					0.09
- *≤ Lower secondary*	37.9	34.3	31.3	32.2	
- *Higher secondary*	27.3	28.5	29.5	27.2	
- *≥ Degree*	34.8	37.2	39.2	40.6	
Employment grade					0.01
- *High*	44.6	49.2	50.1	51.2	
- *Intermediate*	45.8	43.9	44.8	41.6	
- *Low*	9.6	6.9	5.2	7.3	
Diabetes, %	5.8	4.3	6.5	10.6	<0.001

***Chiesa et al 2019 Eur Heart J* doi: 10.1093/eurheartj/ehz189**

Results

Carotid FCWI	Change* in standardised cognitive score per 10 years (95% CI), p-value				
	Global cognitive score	Memory	AH4	Phonemic fluency	Semantic fluency
Effect per 1 SD increase	**-0.02 (-0.04, -0.00) p=0.03**	-0.02 (-0.05, 0.01) p=0.10	-0.01 (-0.02, 0.01) p=0.24	-0.03 (-0.05, 0.00) p=0.06	-0.01 (-0.03, 0.02) p=0.56
Quartiles 1-3	0.0 (Reference)	0.0 (Reference)	0.0 (Reference)	0.0 (Reference)	0.0 (Reference)
Quartile 4	**-0.05 (-0.09, -0.01) p=0.01**	-0.02 (-0.09, 0.04) p=0.45	**-0.04 (-0.07, -0.00) p=0.03**	**-0.09 (-0.14, -0.03) p=0.004**	-0.01 (-0.06, 0.04) p=0.67



Equivalent to 2 years of additional 'cognitive ageing' during follow-up

Adjusted for age, sex, ethnicity, and education

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Results

		Baseline FCWI (N=3191)	
		Lowest 75% (N=2405)	Highest 25% (N=786)
Outcome	The 15% of participants with the greatest cognitive decline over the follow-up	341 (14.2%)	155 (19.7%)
Model	Adjustments	Odds ratio (95% CI)	
M0	Unadjusted	1.0	1.49 (1.21, 1.83)
M1	M0 + age, sex	1.0	1.51 (1.21, 1.88)
M2	M1 + ethnicity, education, employment grade	1.0	1.51 (1.21, 1.88)
M3	M2 + smoking, alcohol consumption, physical activity	1.0	1.50 (1.20, 1.87)
M4	M3 + systolic blood pressure	1.0	1.51 (1.20, 1.91)
M5	M4 + GHQ caseness, hypertension, diabetes, BMI category, history of CVD, atrial fibrillation, physical component score	1.0	1.49 (1.17, 1.88)

Risk of accelerated cognitive decline increased by 50% in individuals with highest FCWI in mid- to late-life

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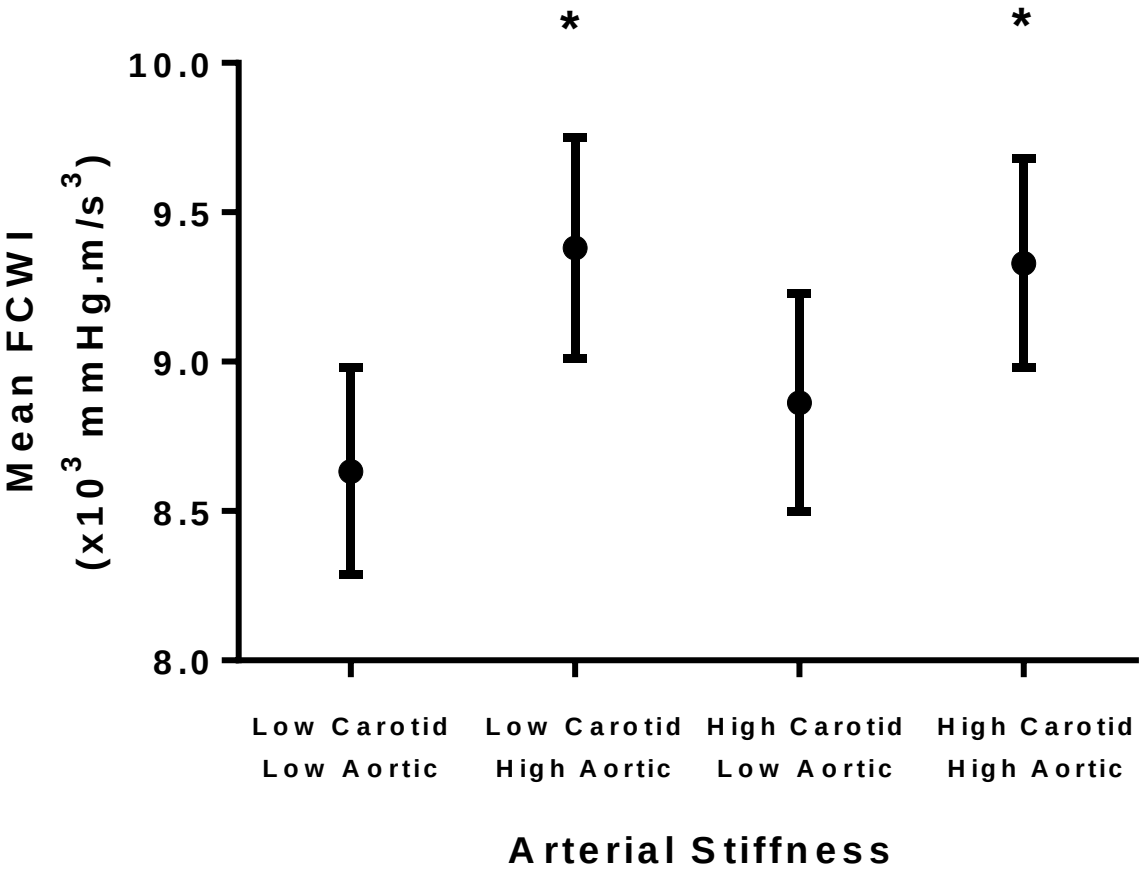
What causes increased FCWI?



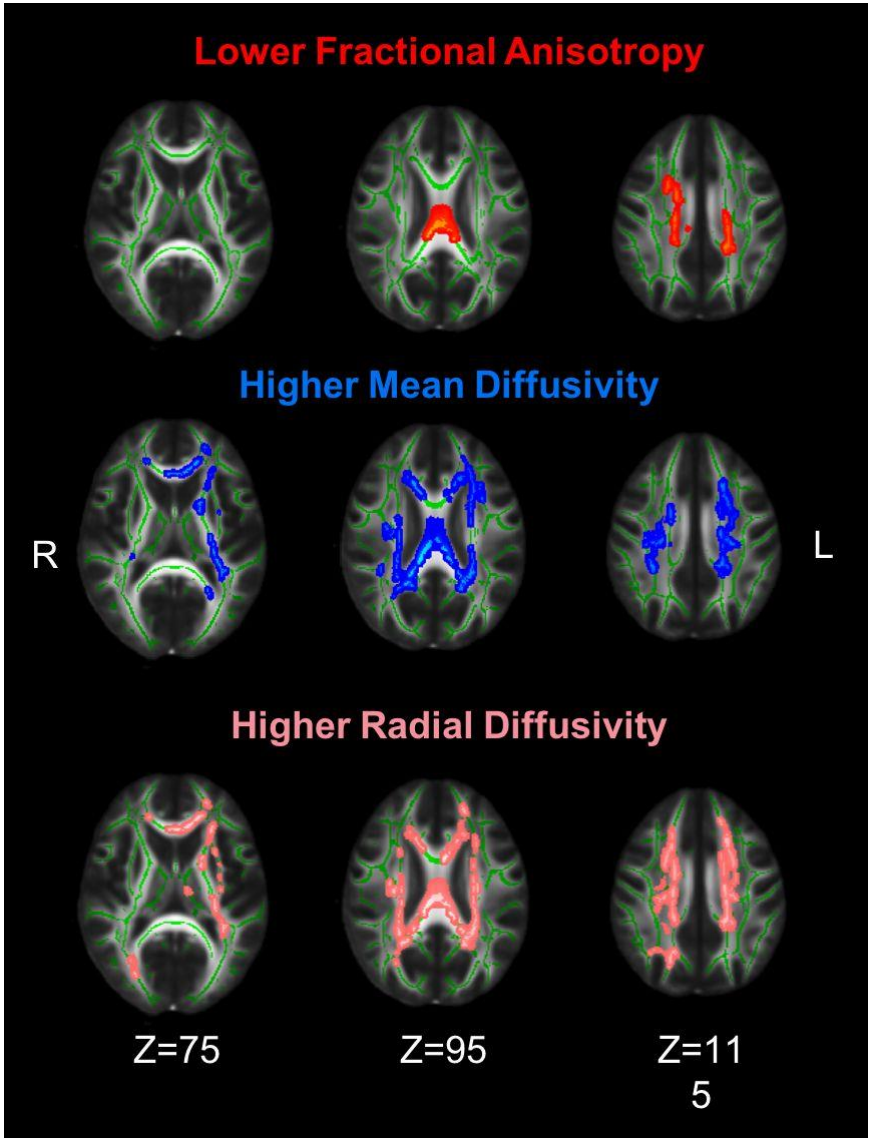
Adjusted for age, sex, ethnicity, BMI, and MAP

Chiesa et al - unpublished data

Structural Changes

- Can we also link wave intensity / arterial stiffness to structural changes within the brains of these participants?

Ongoing, but promising!



Adjusted for age, sex, ethnicity, education, MAP, and BMI

Unpublished data courtesy of Whitehall Imaging Oxford

To summarise

- Carotid wave intensity analysis can be used to quantify the intensity of pulsatile waves transmitted towards the fragile cerebral microcirculation with each beat of the heart.
- High forward compression wave intensity in mid- to late-life predicts accelerated cognitive decline during long-term follow-up.
- Despite their detection in the carotid artery, the presence of these high intensity waves appears to be more closely related to accelerated stiffening of the aorta
- These changes are (probably!) related to structural changes within the brain detected by MRI, which may mediate the relationship between systemic arterial changes and cognitive decline.

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