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The role of the vascular system in flavonoid-induced cognitive enhancement

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Centre for Integrative Neuroscience and Neurodynamics

Institute for Cardiovascular and Metabolic Research

University of Reading, UK

Flavonoid intake is associated with a better cognitive evolution

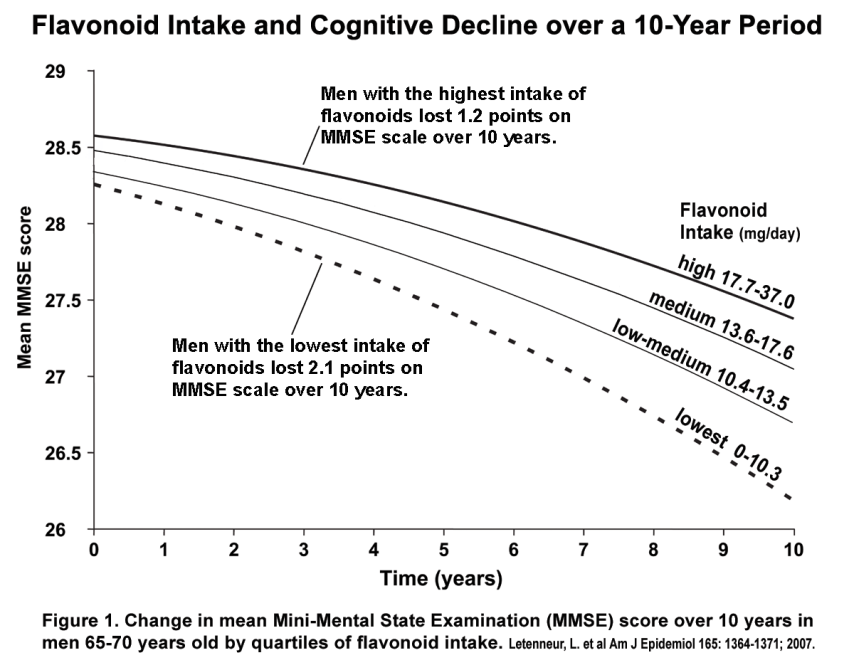
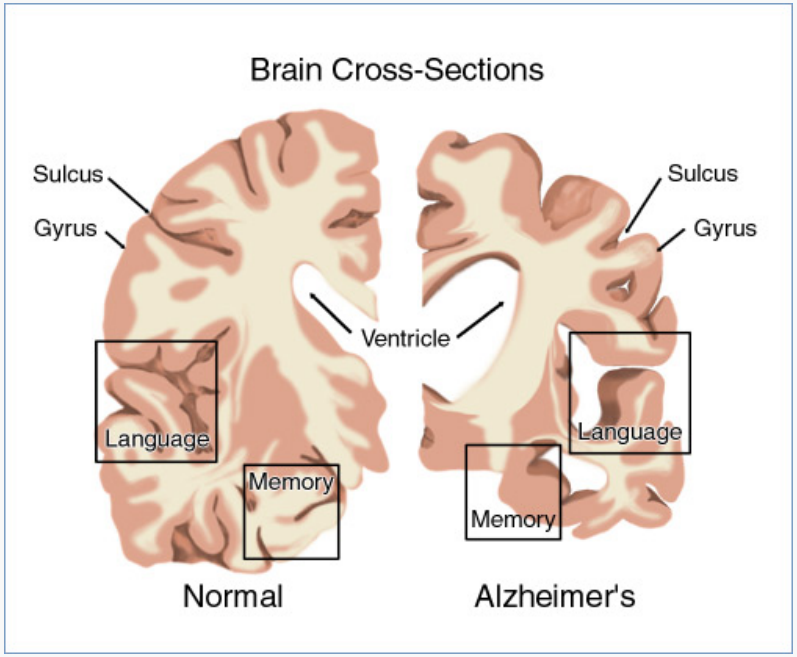


Figure 1. Change in mean Mini-Mental State Examination (MMSE) score over 10 years in men 65-70 years old by quartiles of flavonoid intake. Letenneur, L. et al Am J Epidemiol 165: 1364-1371; 2007.



Reduction in global cognitive decline with increasing daily flavonoid intake

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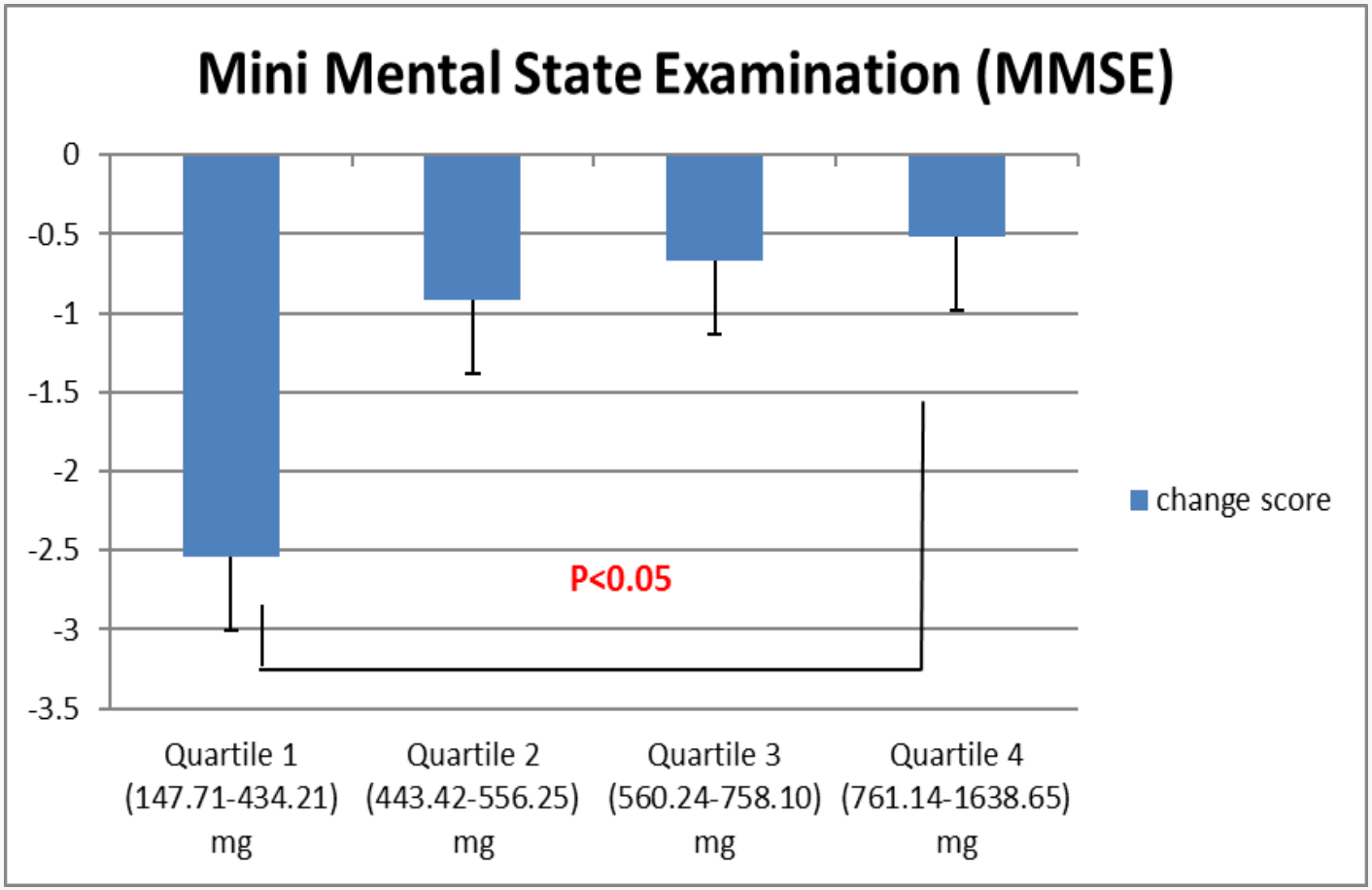

Measurement of multiple Cognitive domains

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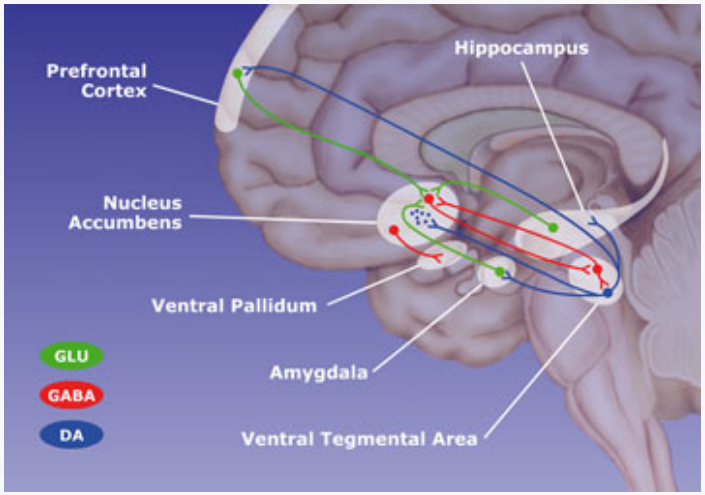
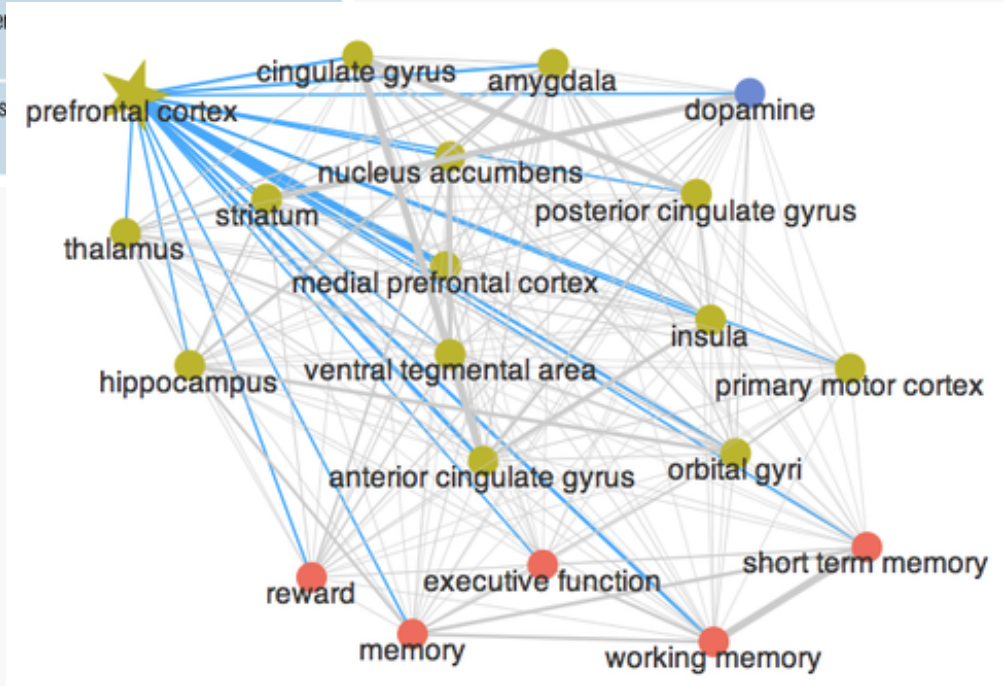
Primary domains of human cognition

Cognitive measure	Definition
Working memory	Temporary online storage of information and mental manipulation of information
Attention (sustained focused attention or vigilance)	Ability to maintain a consistent behavioral response throughout a continuous or repetitive activity
Speed of processing	More basic cognitive processes involving speed of performance, whether perceptual or motor
Verbal learning and memory	The ability to acquire and retain ve verbal instructions
Visuospatial learning and memory	The ability to acquire and retain vis figures and maps





Impact of cocoa flavanol supplementation on cognitive performance

- 103 healthy 65-80 yrs
- Male
- Assessed as cognitively healthy at baseline

- Acute 0-2 h intervention

- Medium-term intervention (12 weeks)

	High CF product	Low CF Product
Packet code	252	639
Packet size, g	30	30
mg Cocoa Flavanols (DP 1-10)	494	29
epicatechin, mg	89	3
catechin, mg	21	3
dimers-decamers, mg	384	20
Calories	113	112
Total fat, g	1	1
Saturated fat, g	1	1
Cholesterol, mg	5	5
Sodium, mg	197	204
Total Carbohydrates, g	16	16
Dietary Fiber, g	3	4
Sugars, g	10	9
Protein, g	9	9
Caffeine, mg	15	17
Theobromine, mg	185	176
Potassium, mg	507	573
Calcium, mg	243	225
Iron, mg	2	4
Phosphorus, mg	272	247
Magnesium, mg	82	74
Zinc, mg	1	1
Copper, mg	0	0
Manganese, mg	0	0

Cocoa flavanol intervention acutely (2h) improves executive function and episodic memory performance

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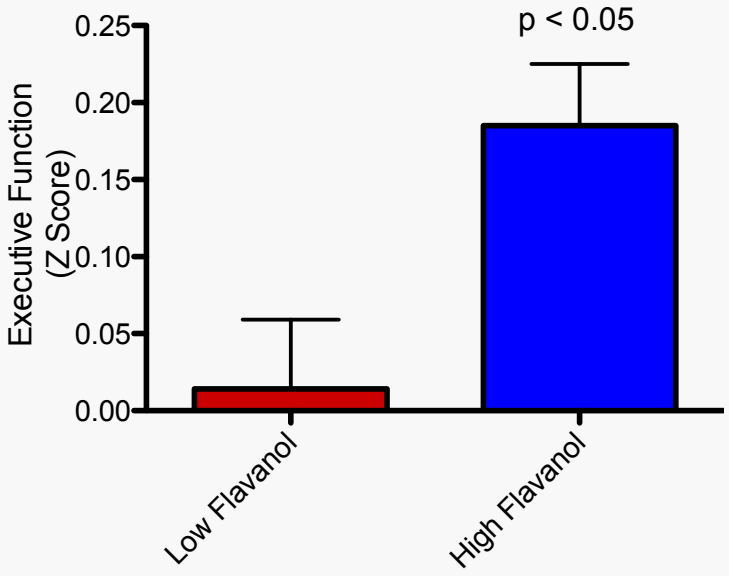
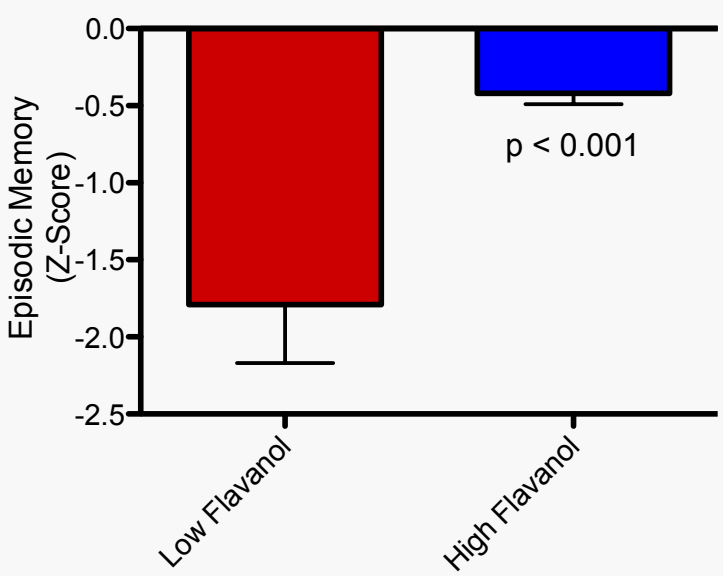
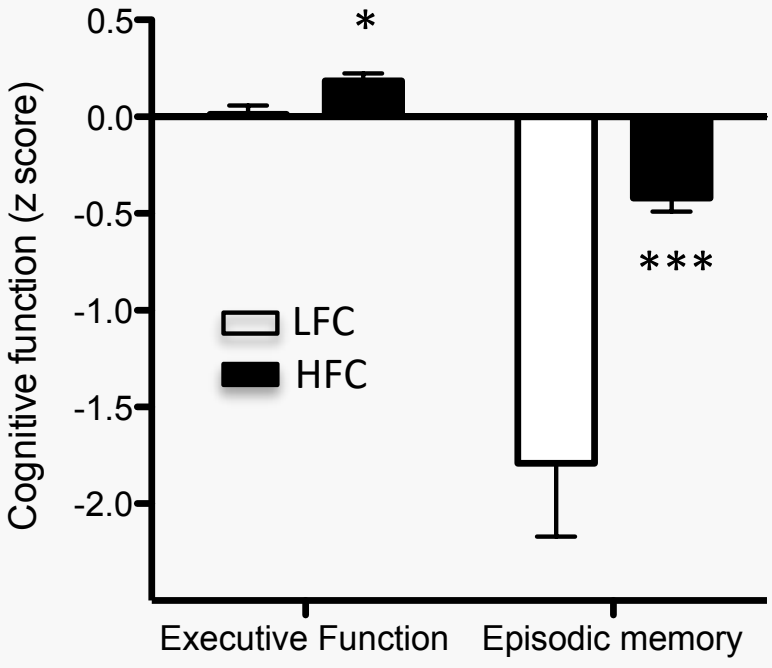
Executive Function
z-score from 5 tests

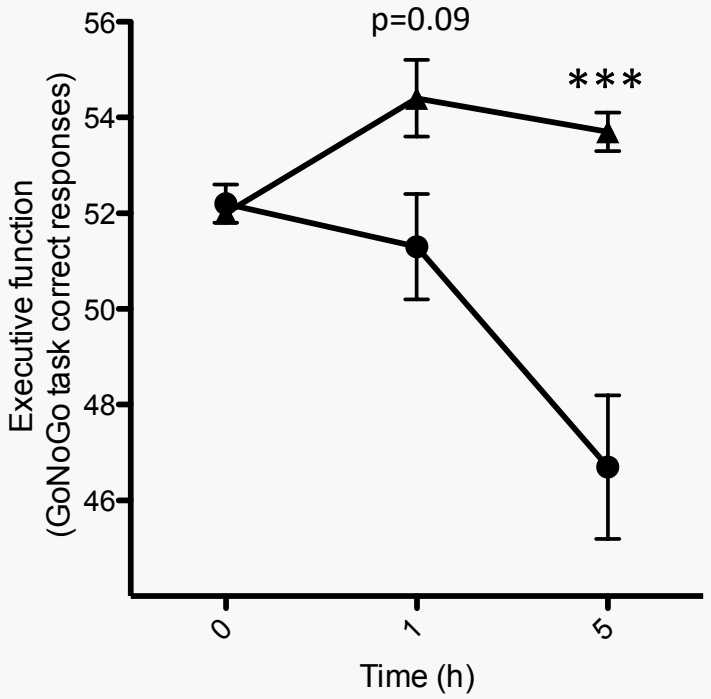


Episodic memory
z-score from 4 tests



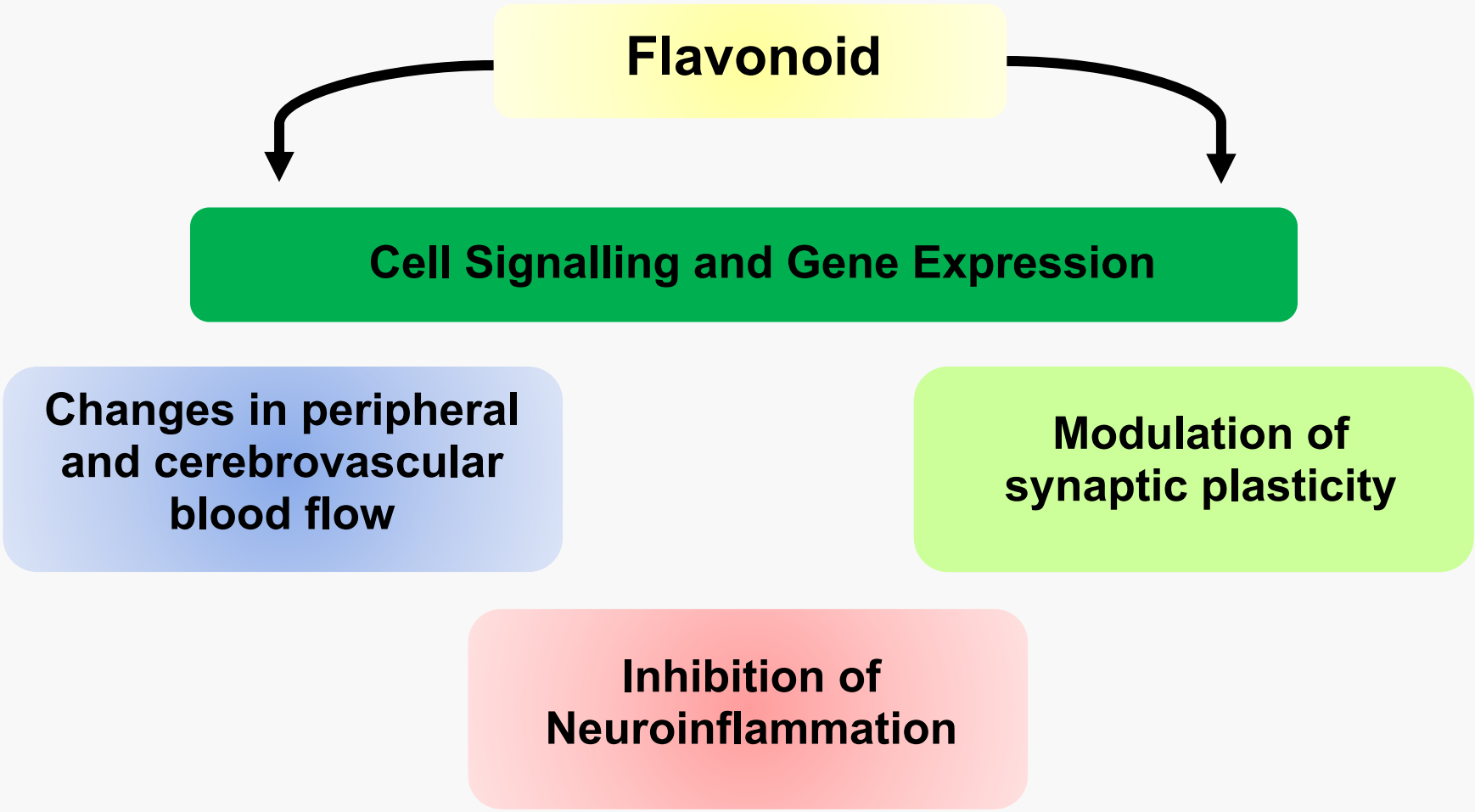
Cocoa (flavanol) and berry (anthocyanin) intervention acutely improves human executive function and episodic memory





BBSRC grant (Grant ref. BB/F008953/1): Enhancement of learning and memory by flavonoids
[Start date: 01-04-08, end date: 31-03-11]: £485,357

How do flavonoids induce improvements in human cognition?



Cellular and molecular underpinning of flavonoid action on cognition

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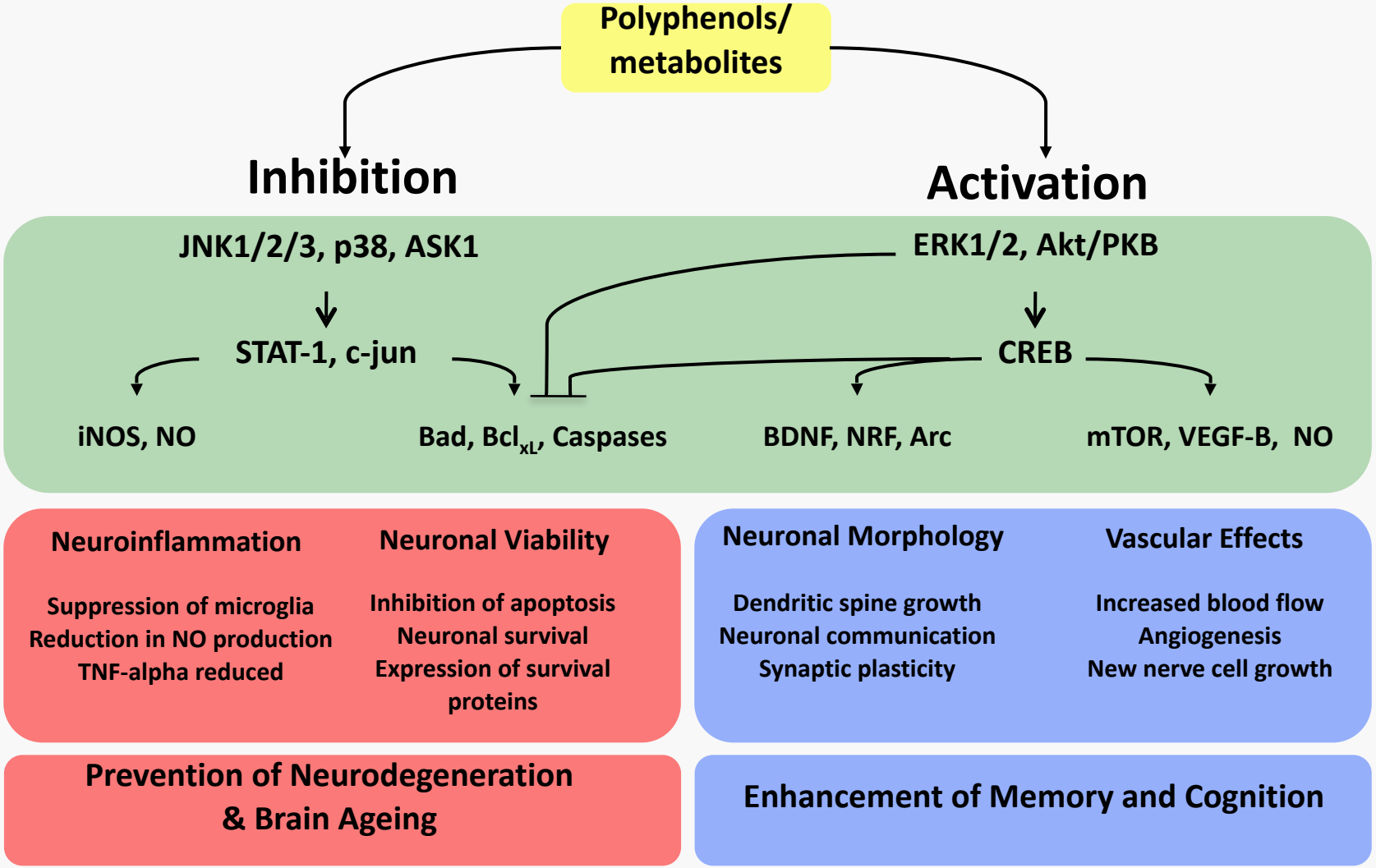

BB and pure flavonoids induce BDNF expression in the hippocampus

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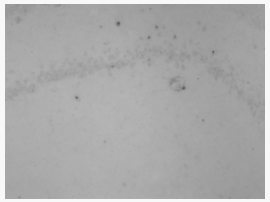
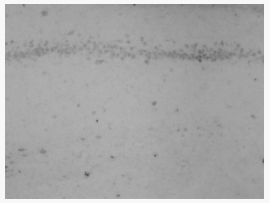
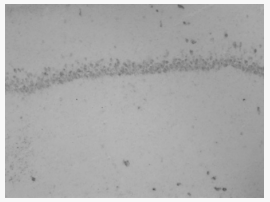
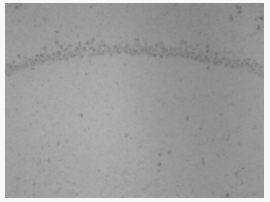
BDNF mRNA

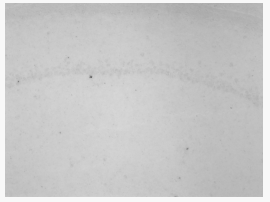
CA1 region
of hippocampus



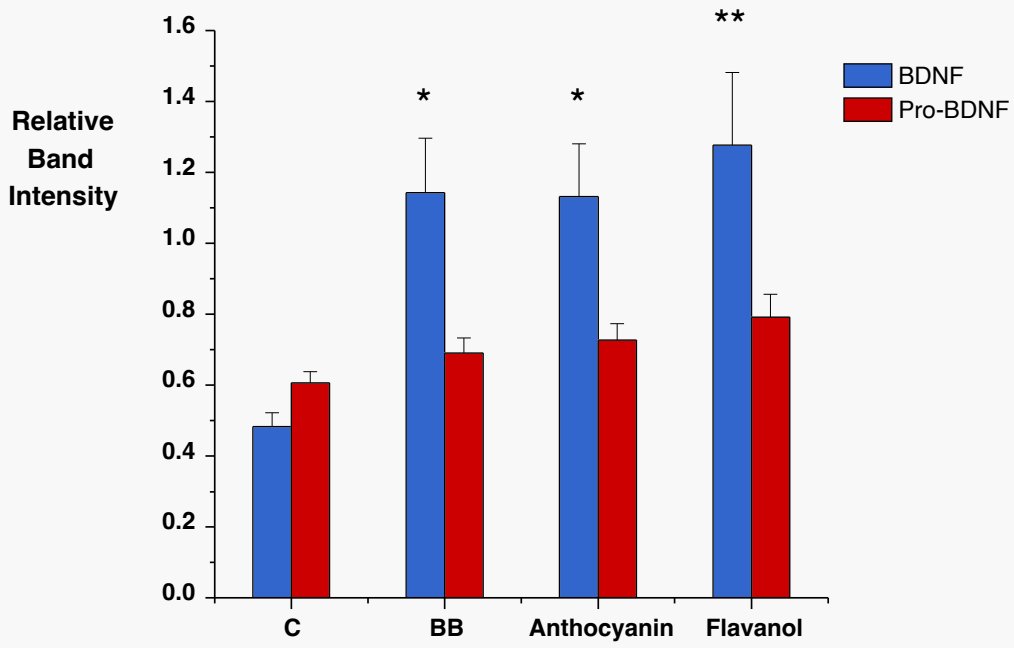








Hippocampal BDNF protein



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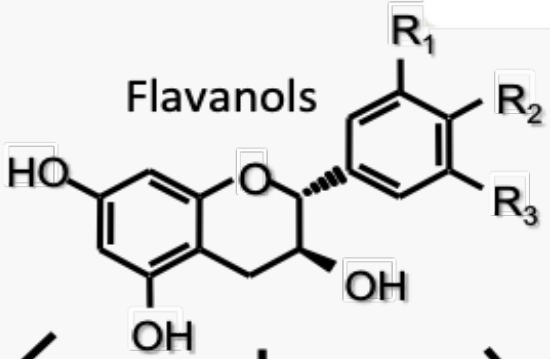
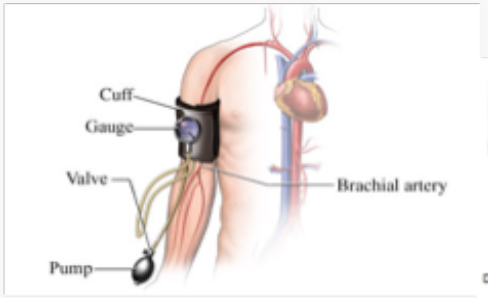
Cocoa

Blueberry?

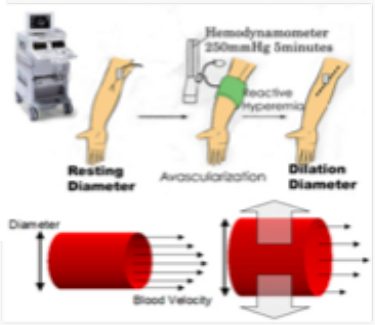
Tea

Flavanols

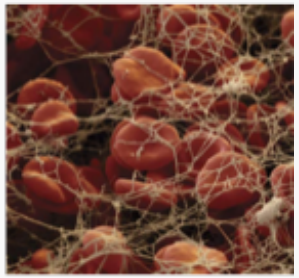




Lower Blood Pressure



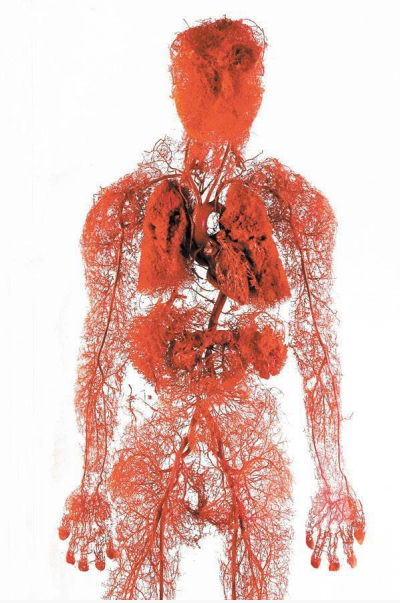
Improved Vascular Function



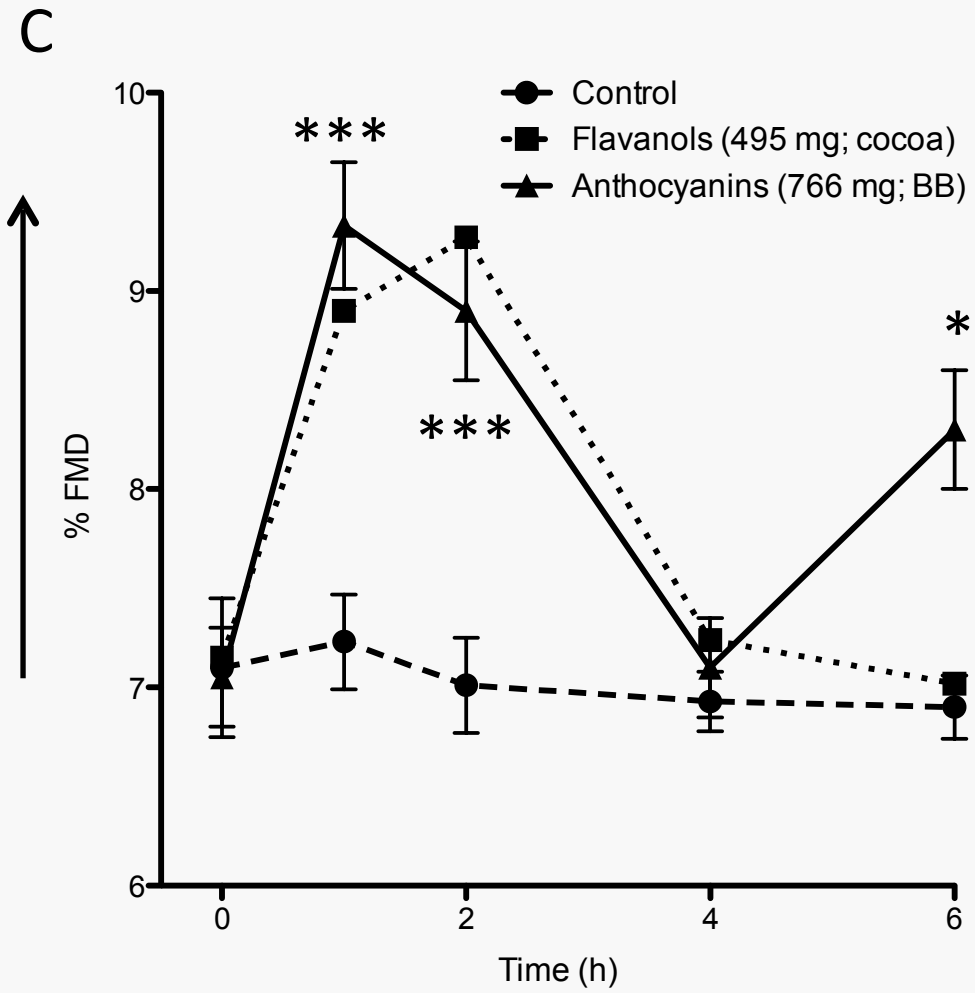
Decreased Blood Clotting

Reduced Risk of Cardiovascular Disease

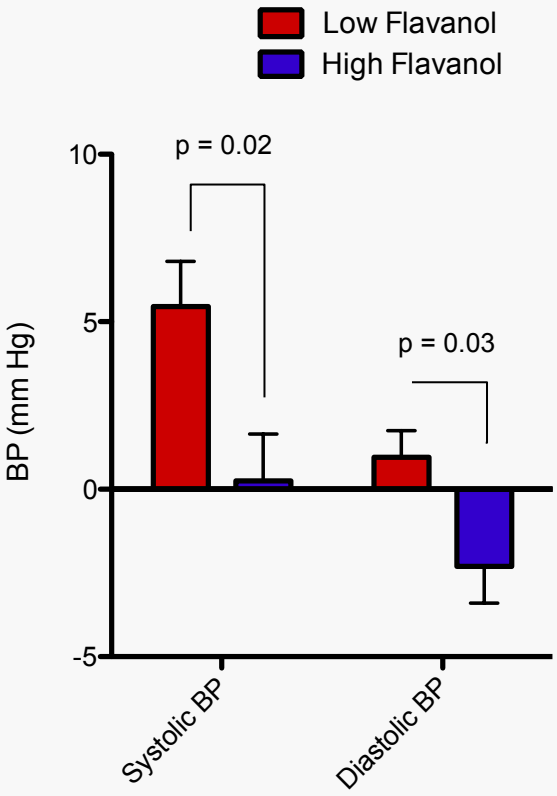
Flavanols (cocoa) and anthocyanins (blueberry) improve peripheral blood flow



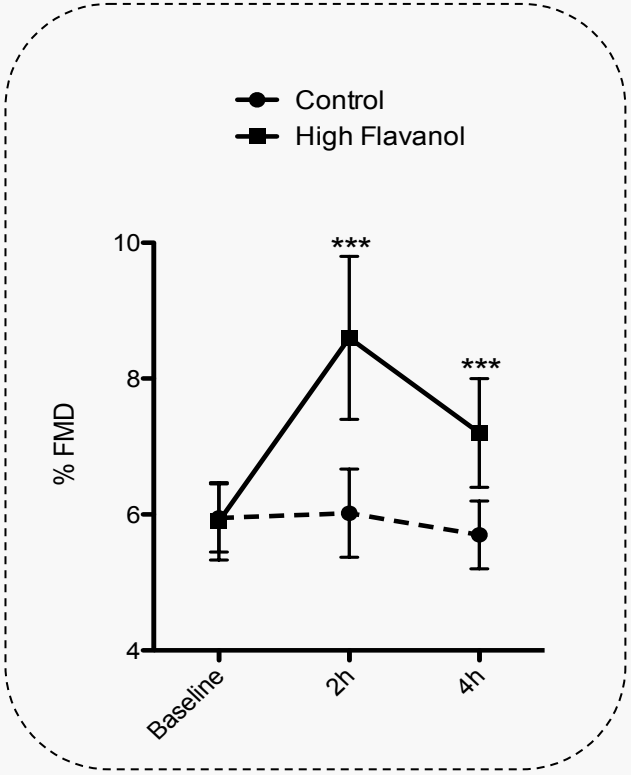
- Better blood perfusion
- Reduction in BP
- Reduced vascular stiffness



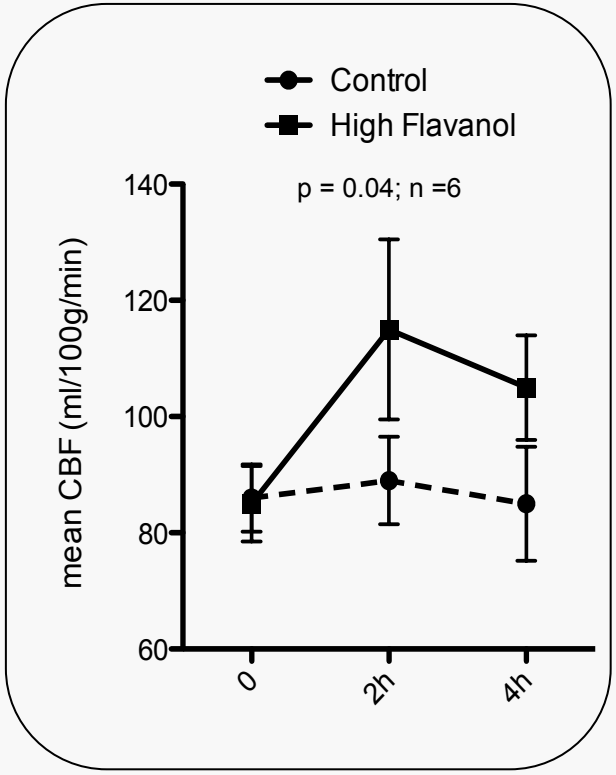
Acute cognitive improvements induced by flavanols may be linked to changes in cerebrovascular blood flow



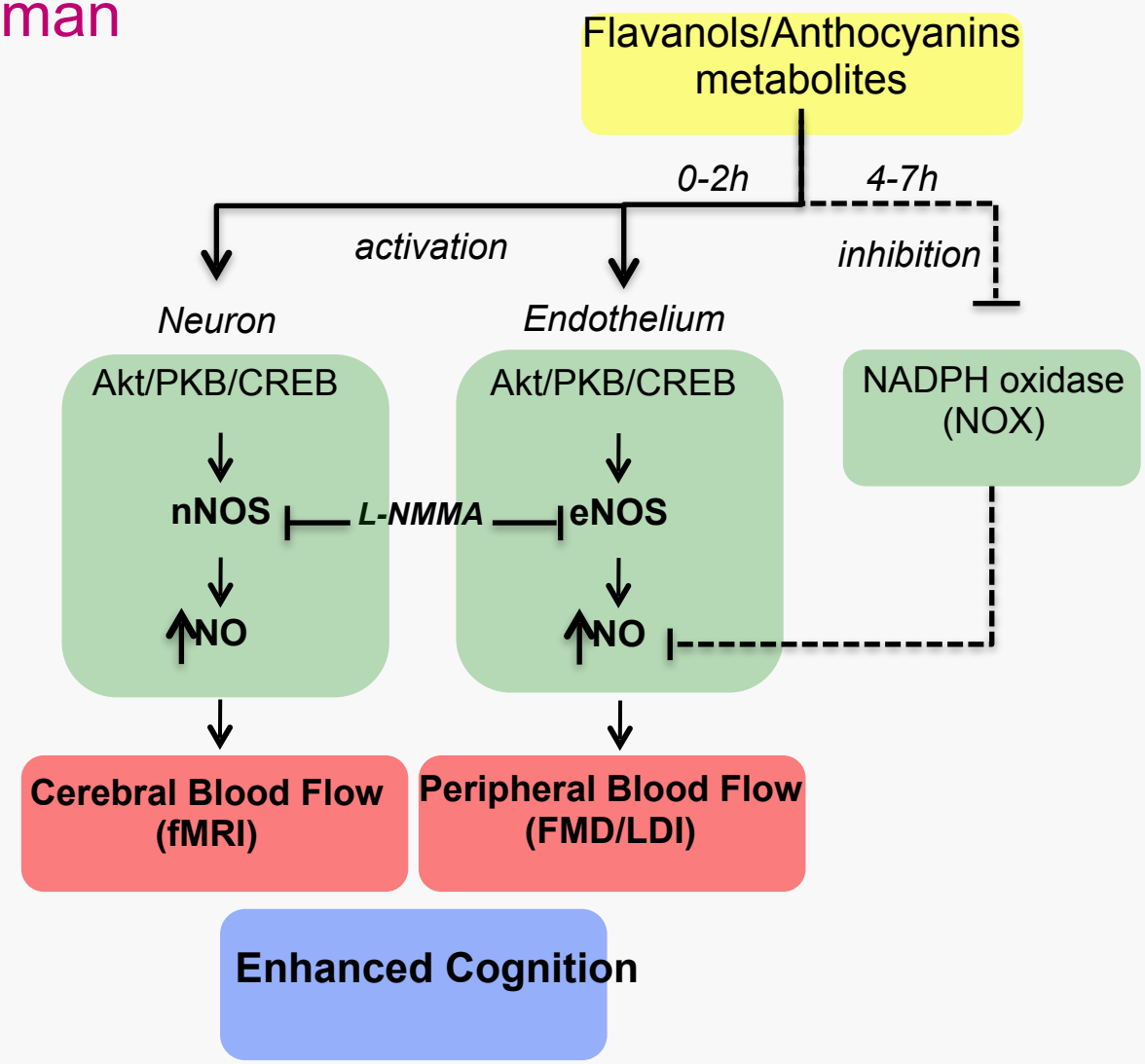
Peripheral vascular response



Cerebrovascular response



Hypothesis: Flavanol/ anthocyanin induced enhancement of human cognition is mediated by the vascular system



Double masked, cross-over RCT to investigate whether acute improvements in cognition are mediated by nitric oxide

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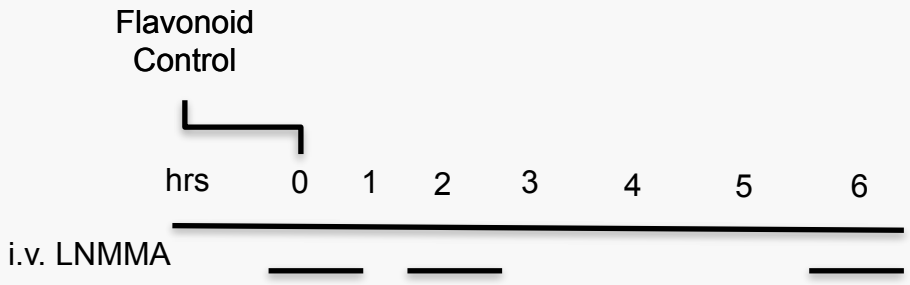

1° Cognitive testing	+		+				+
2° fMRI	+		+				+
FMD	+		+				+
Plamsa NO	+	+	+	+	+	+	+
NOX	+	+	+	+	+	+	+
	+	+	+	+	+	+	+
3° Plasma Flavo metabolites							

- **32 healthy m/f volunteers**
- **3 arm, acute intervention**
- **Cross over design**

- **Control (cellulose)**

- **Flavonoid**
  (-)-Epicatechin (1 mg/kg BW)
  Delphinidin (1 mg/kg BW)

- **Flavonoid + L-NMMA**
  (1 mg/kg/min; 3 min)

Partial attenuation of (-)-EC/delphinidin induced cognition via pharmacological eNOS inhibition (1h)

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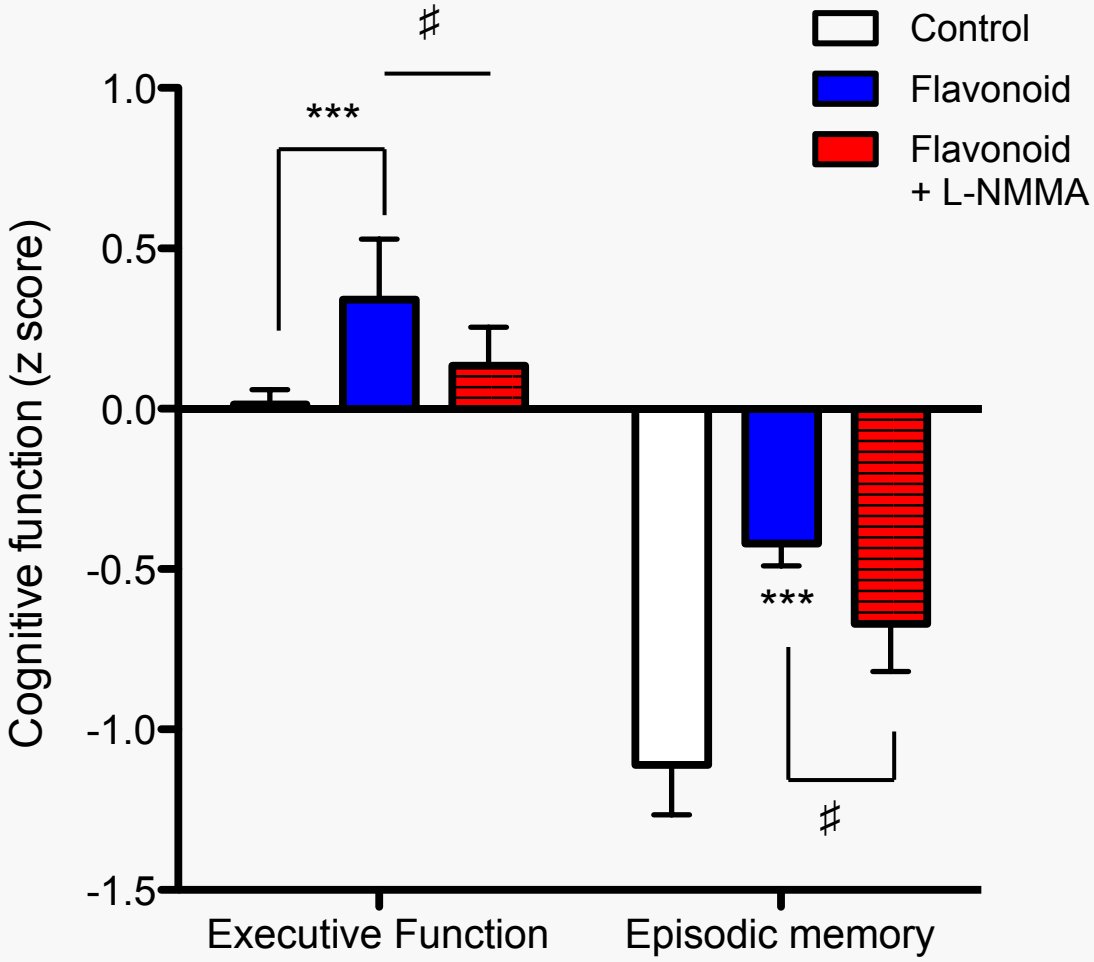
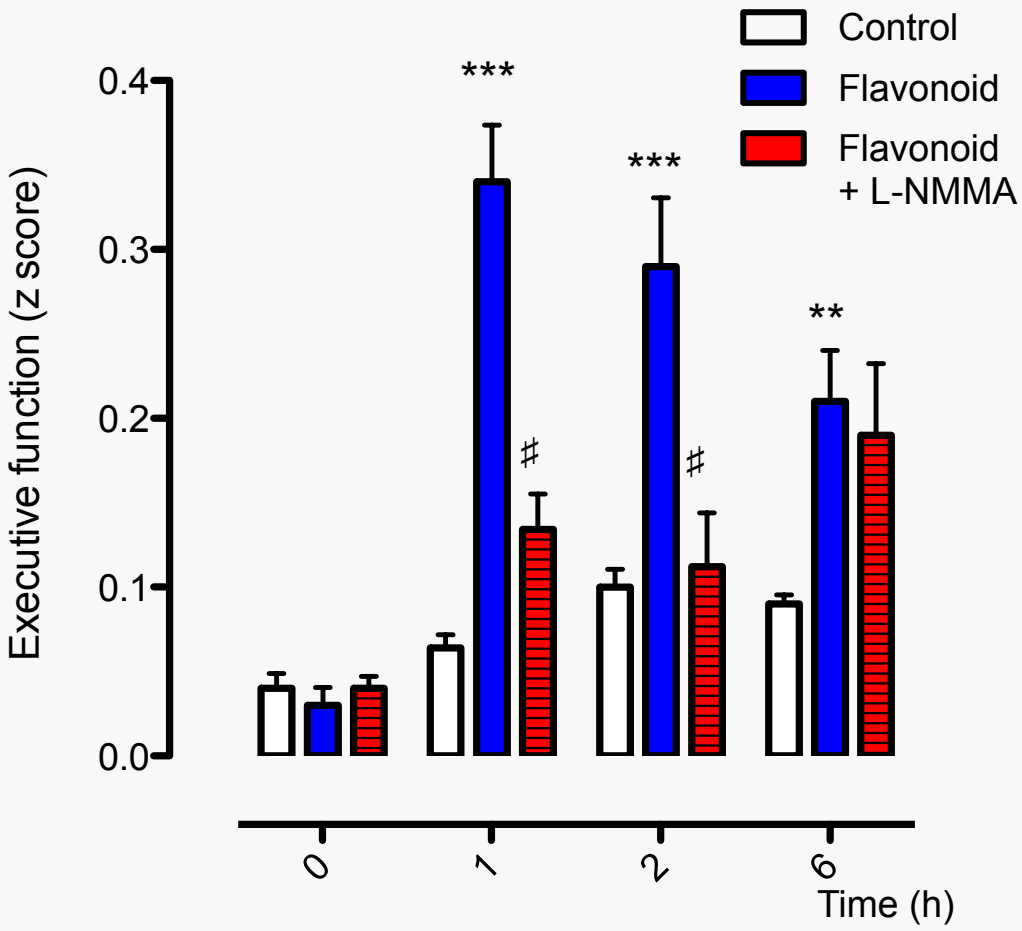
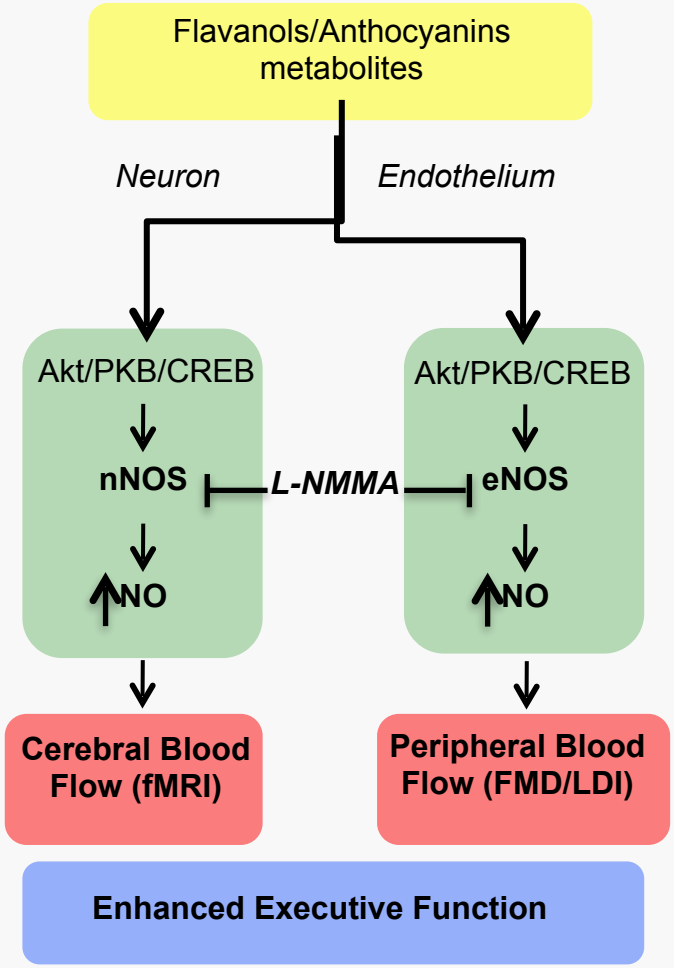


*** vs. control; # vs. flavonoid alone

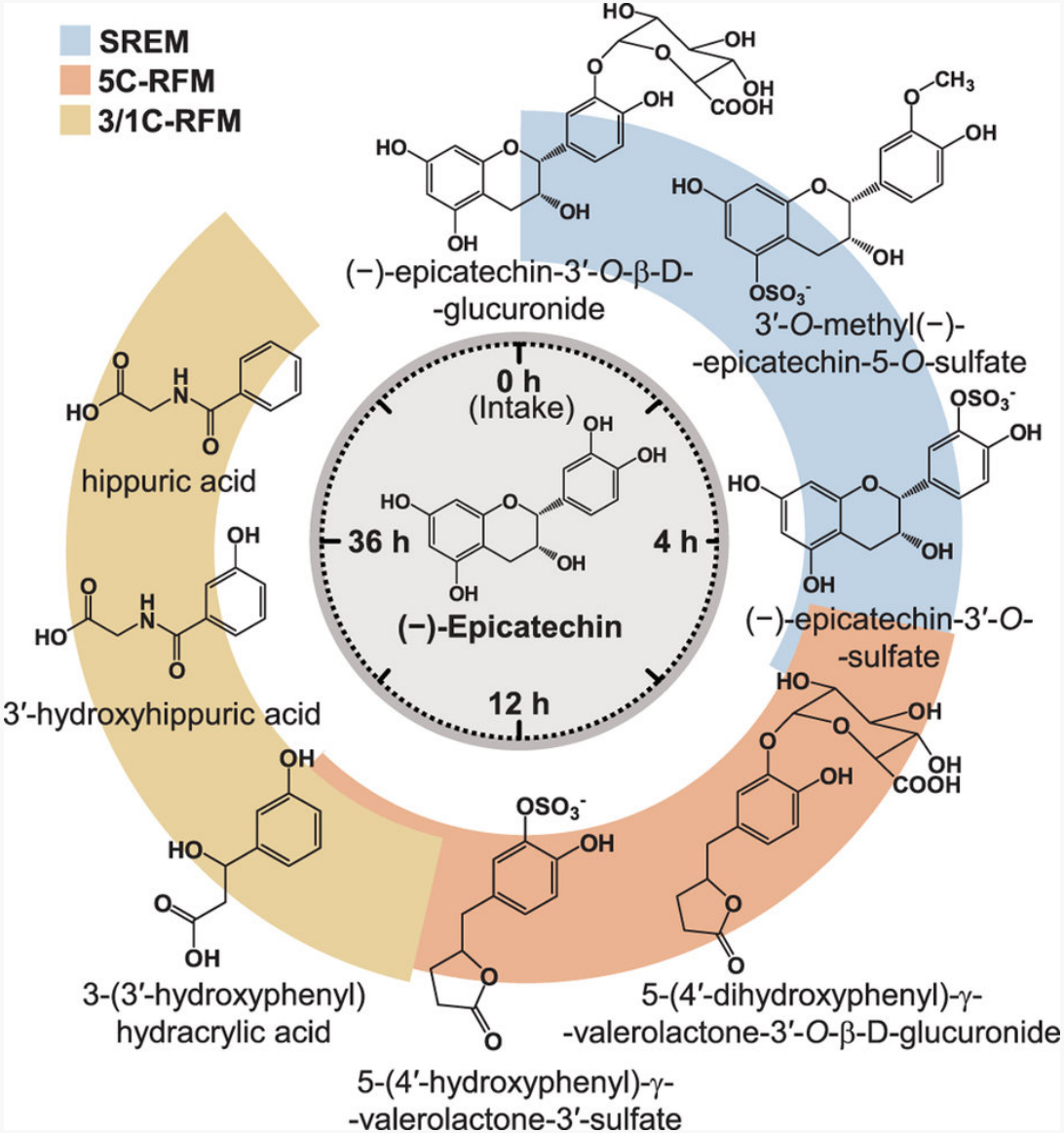
Inhibition of eNOS blocks early flavonoid-induced executive function but not late



***, ** vs. control; # vs. flavonoid alone



Flavanol metabolism



eNOS inhibition partially blocks flavonoid-induced peripheral blood flow

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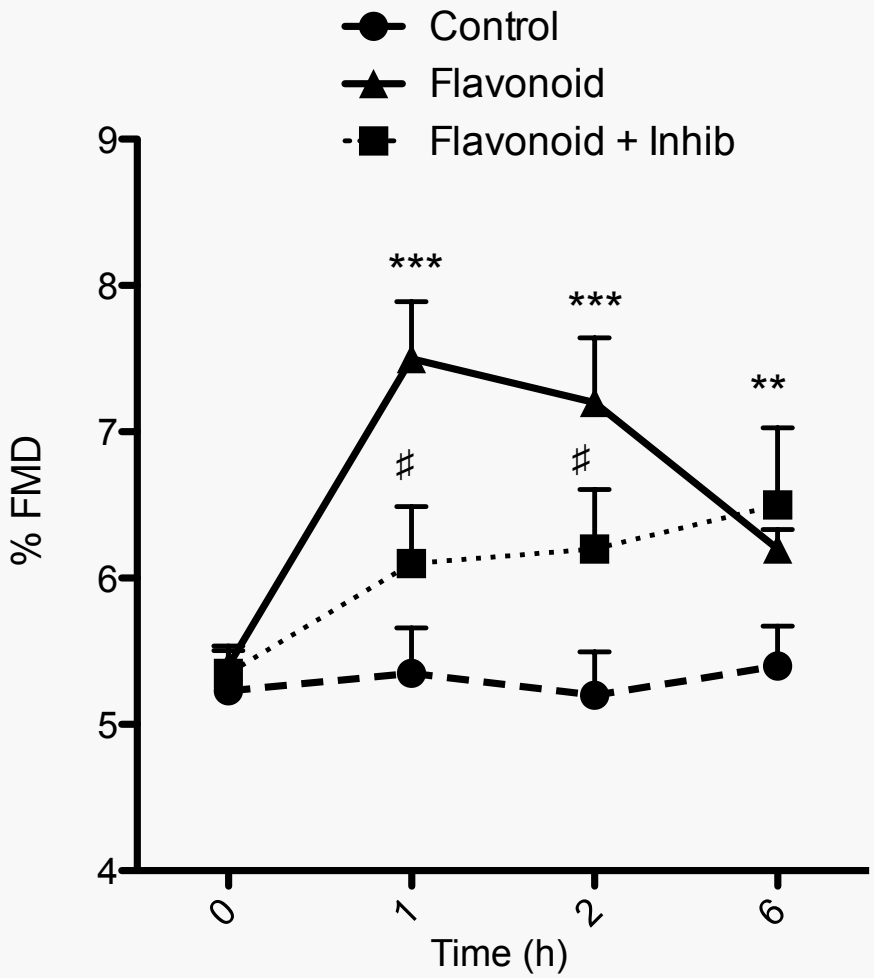
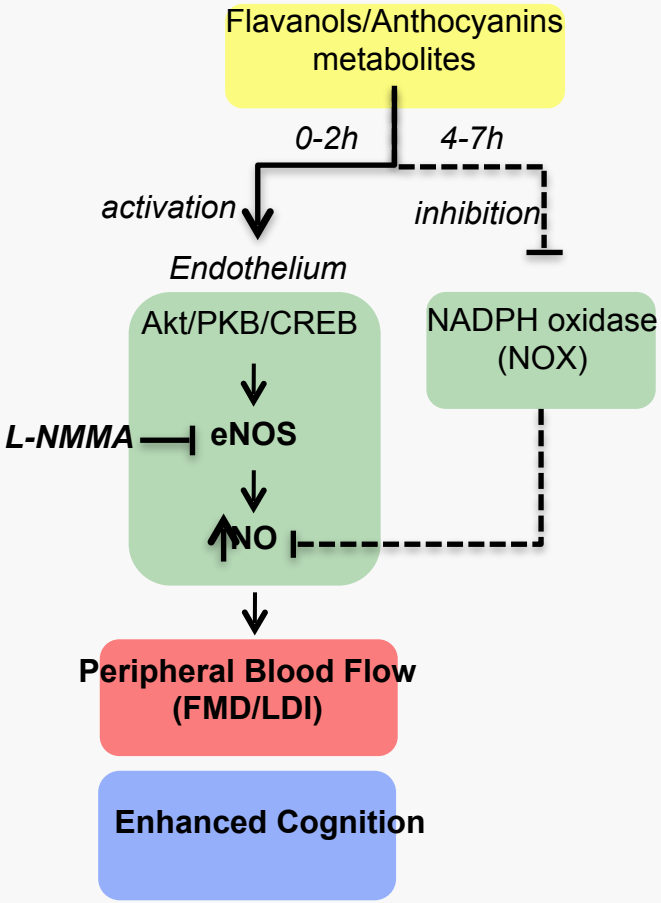


***, ** vs. control; # vs. flavonoid alone



Flavonoid-induced increases in mean CBF are attenuated by eNOS/nNOS inhibition

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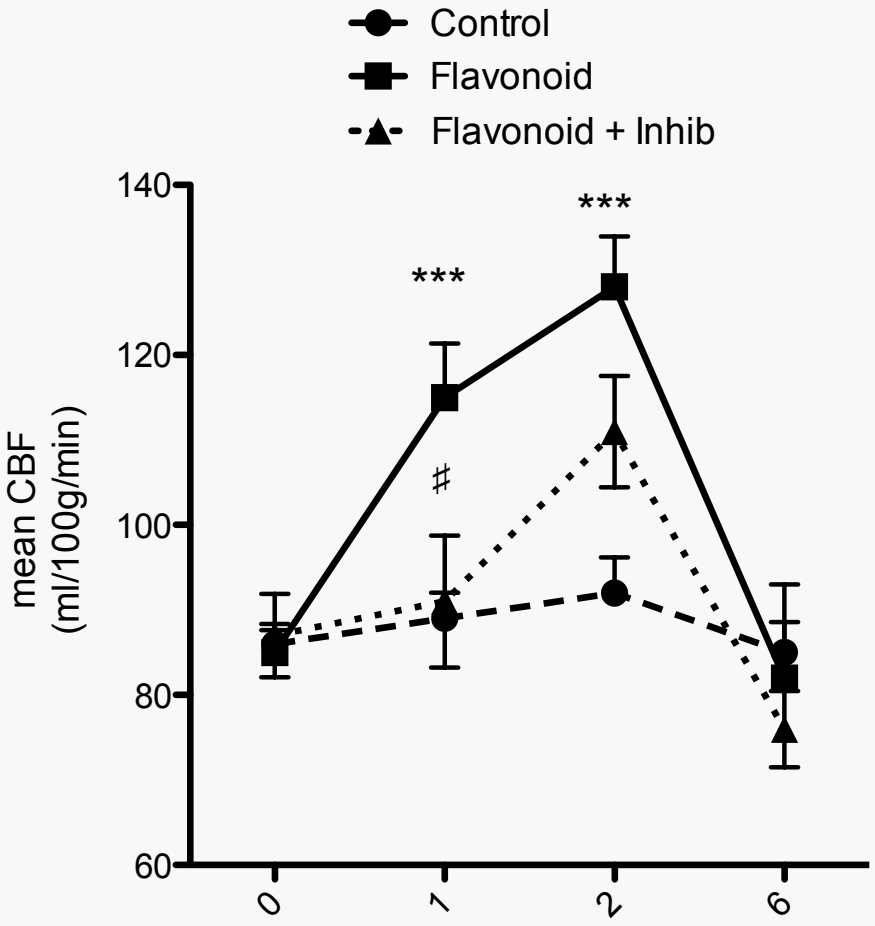
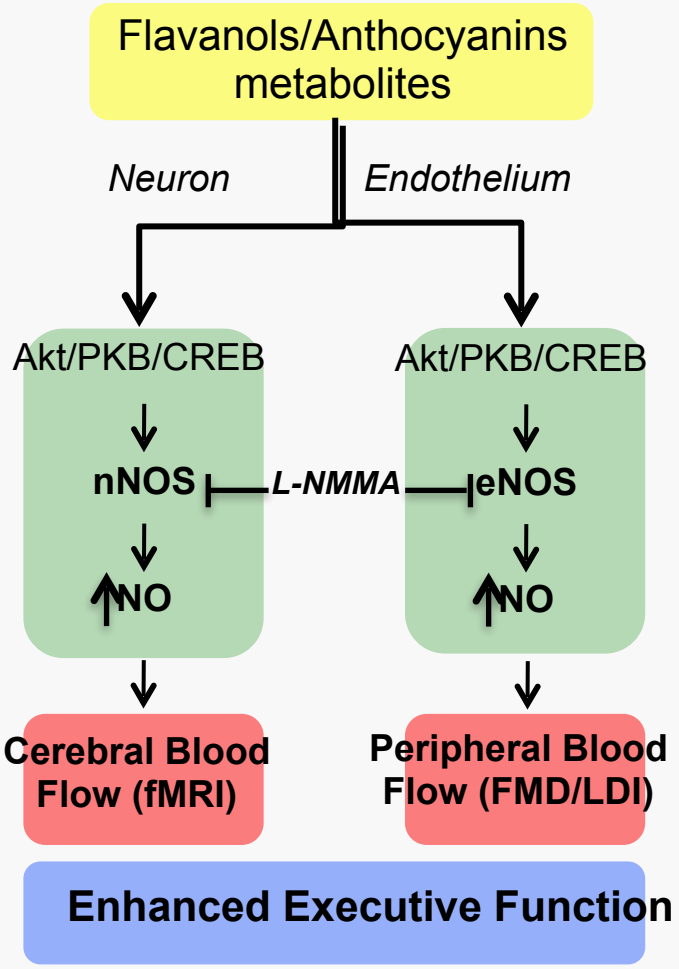
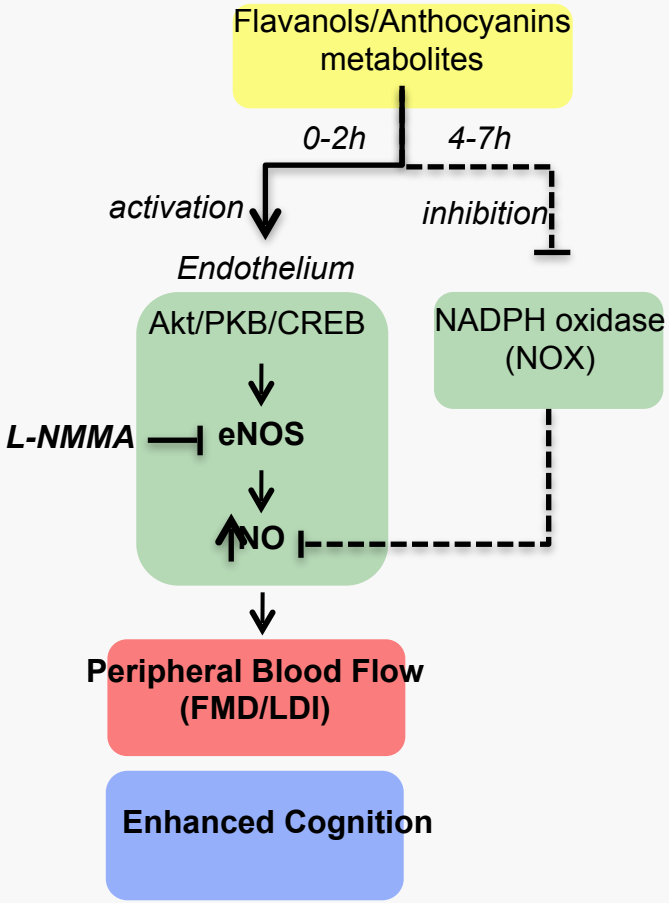
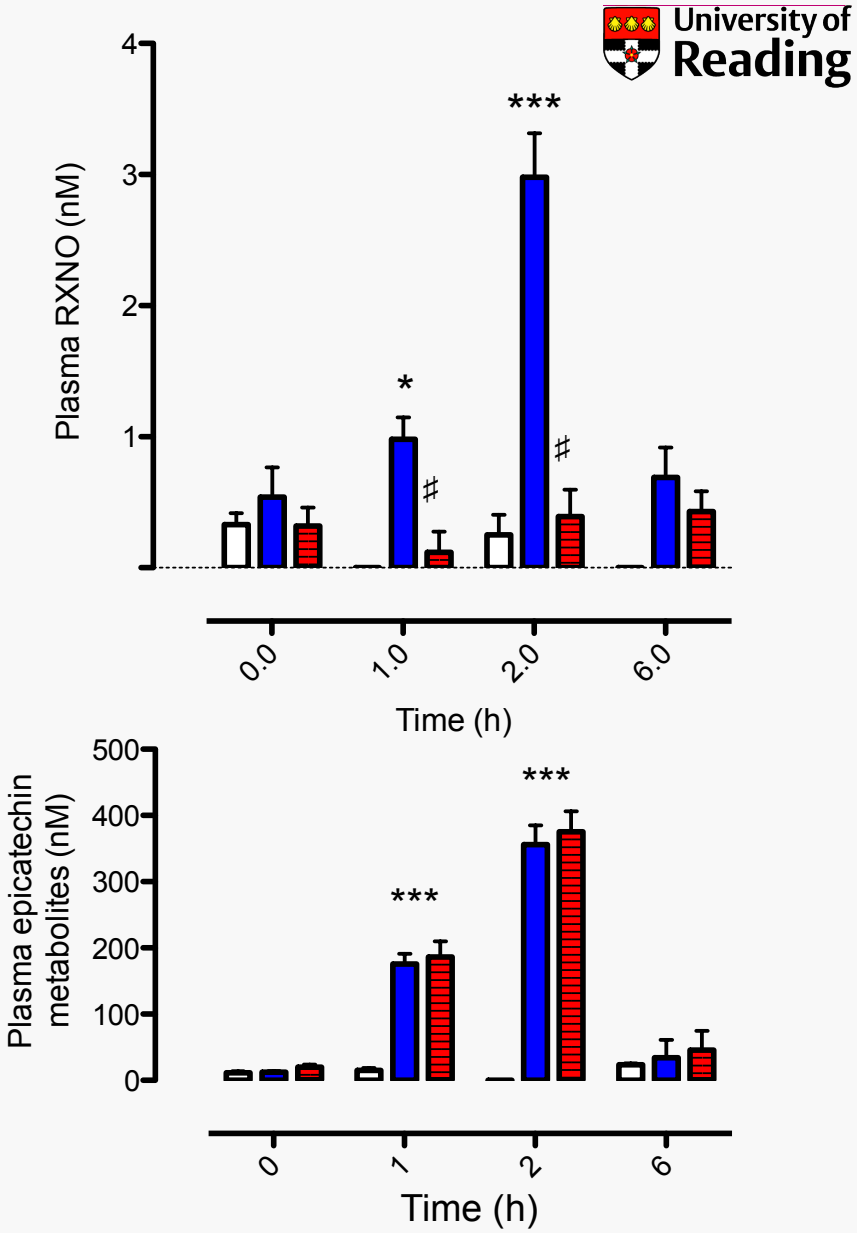


*** vs. control; # vs. flavonoid alone



Plasma NOx but not flavanol metabolism are modulated by L-NMMA





***, * vs. control; ♯ vs. flavonoid alone

Time-series analysis of ‘resting state’ ASL data
- flavanol intervention v control: baseline to 2h

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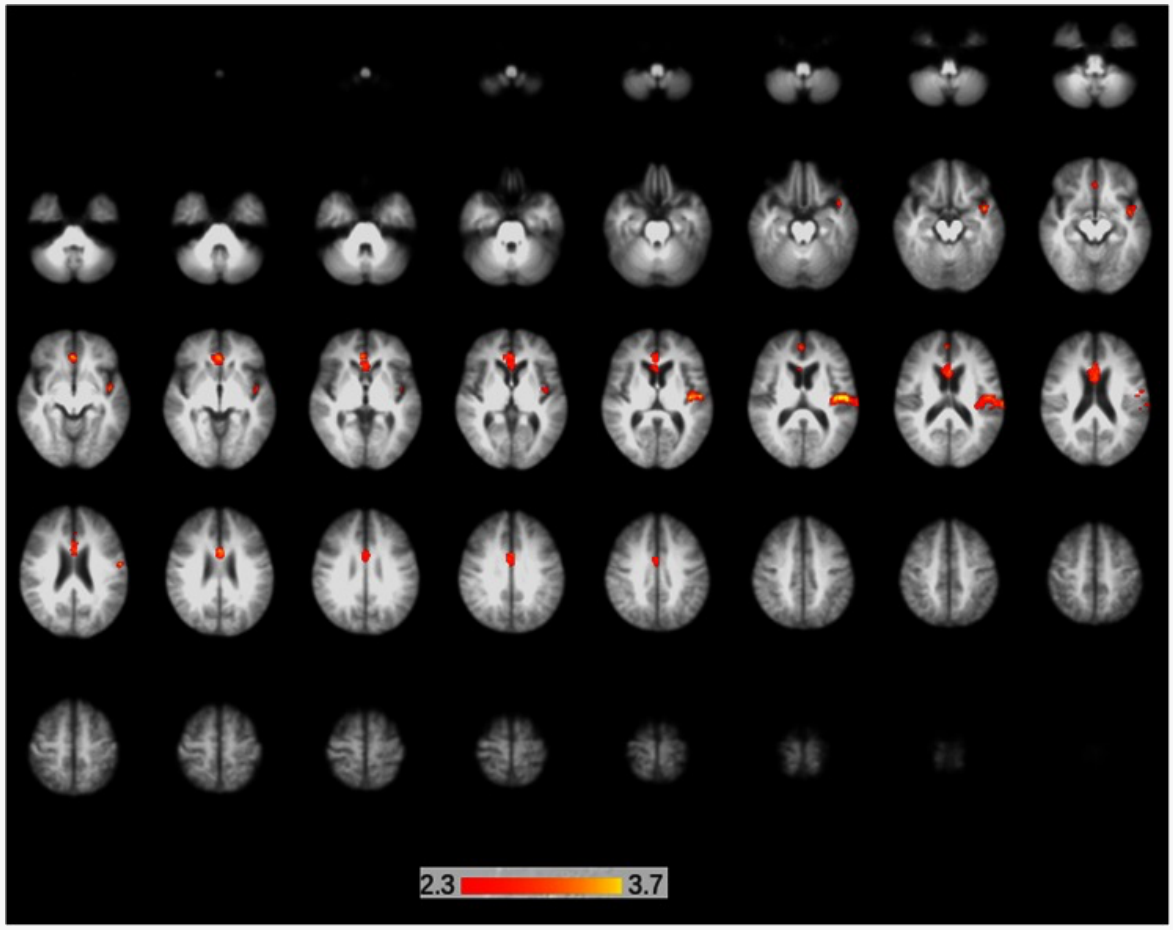

Significantly greater change in blood perfusion following the high flavanol drink compared to the low flavanol drink in two clusters; the ACC and the central opercular cortex of the left parietal lobe down to a sub-cluster in the temporal pole.

The anterior cingulate cortex (ACC) and autonomic control of blood pressure

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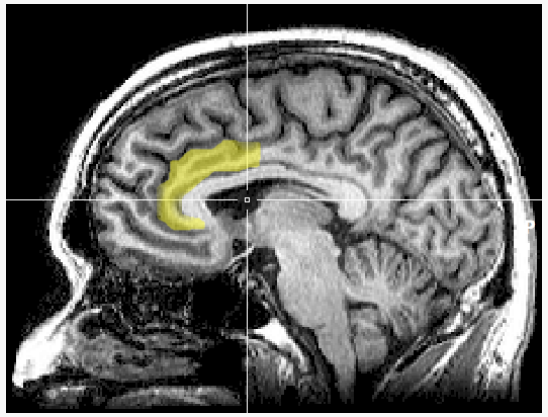
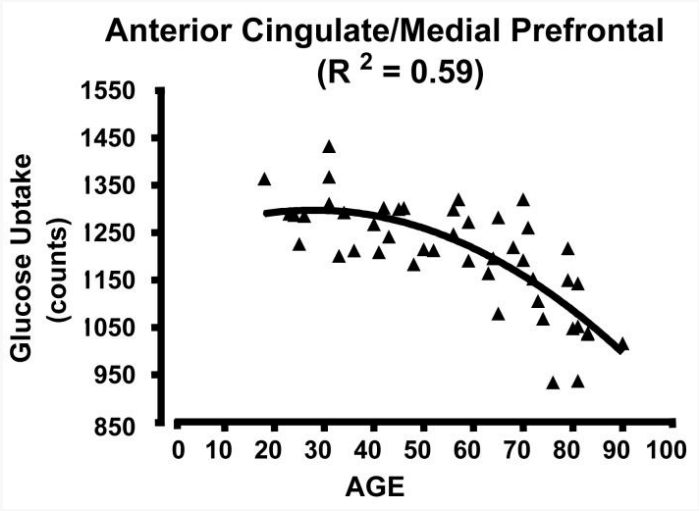
- ACC involved in attentional demand and executive control, such as reward anticipation, decision-making, impulse control and emotion.
- The ACC is known to play a role in control of the autonomic nervous system, including regulation of blood pressure and heart rate.
- Electrical stimulation of any division of the ACC elicits a significant fall in blood pressure.
- Age is known to be negatively correlated with blood flow and neural activity in dorsal and rostral ACC regions.





Changes in CBV-fMRI before and 12 weeks after daily flavanol intake

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COSMOS Shows Promise of Cocoa Flavanols for Reducing Cardiovascular Risk

COSMOS is the first large-scale trial to test cardiovascular benefits of cocoa flavanols

	Including all participants in the analysis, the results in the cocoa flavanol supplement group (vs. placebo group) show:	Excluding participants who admitted to not taking their study pills in accordance with the study protocol, the results demonstrated that the cocoa flavanol supplement group had:
Primary endpoint: Total count of all cardiovascular events (heart attacks, strokes, cardiovascular surgeries and deaths)	**10%** Reduction (not statistically significant)	**15% Reduction**
Secondary endpoint: Deaths from cardiovascular disease	**27% Reduction**	**39% Reduction**
Additional analysis: Total number of major cardiovascular events (heart attacks, strokes and deaths)	**16% Reduction**	**24% Reduction**

The cocoa flavanol intervention was well-tolerated and safe

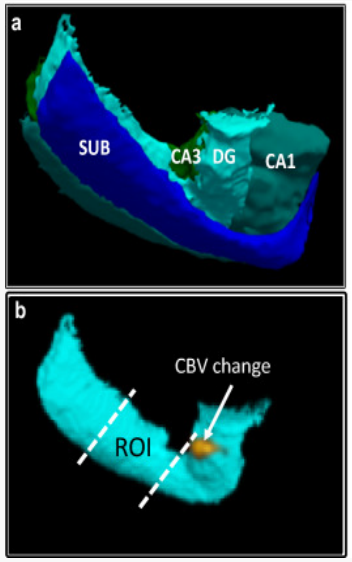
COSMOS: A rigorous landmark study

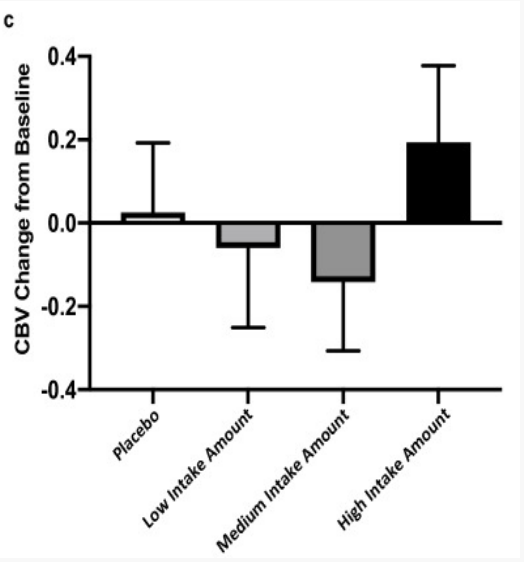
21,000+ healthy men & women aged 60+ up to **five years**

Randomized, double-blind, placebo-controlled study

Independently planned and led by researchers at Brigham and Women's Hospital, an affiliate of Harvard Medical School

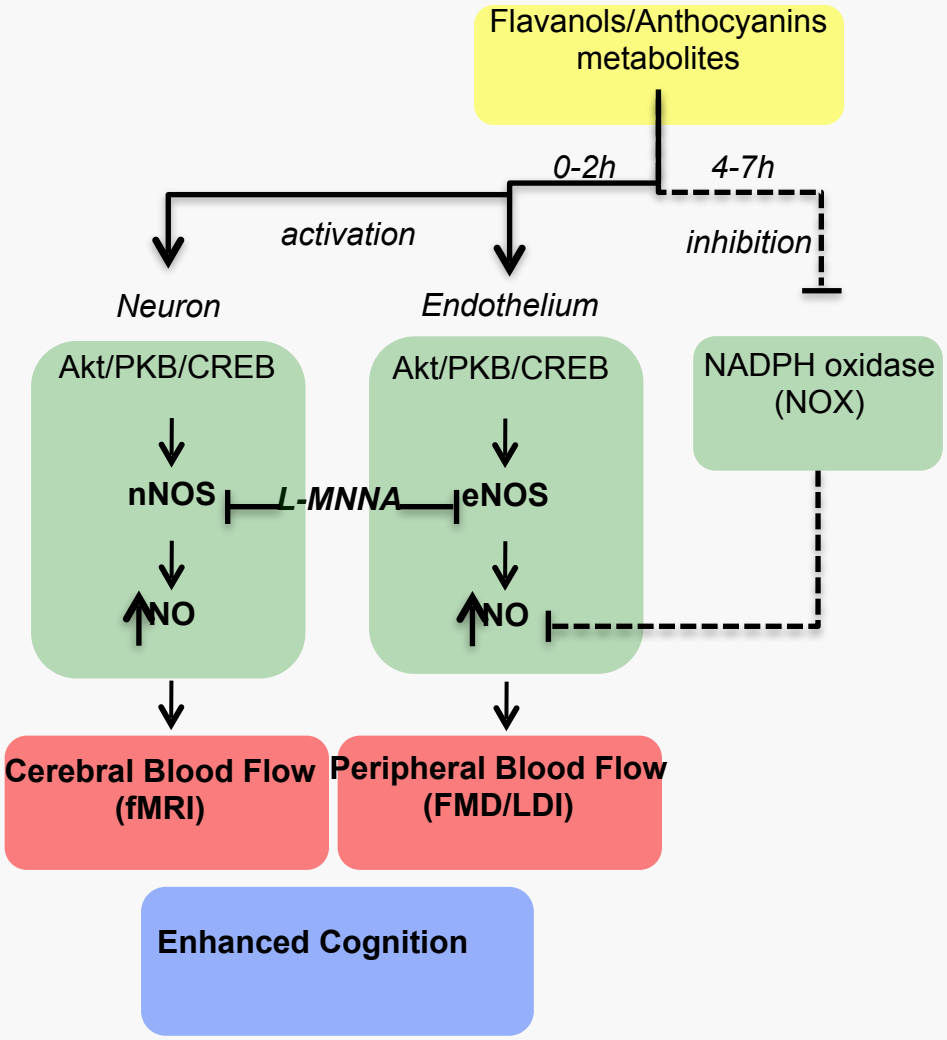
COSMOS was supported by **Mars Edge**, a segment of Mars dedicated to nutrition research and products, **Pfizer Consumer Healthcare** (now part of GSK Consumer Healthcare) and the **National Institutes of Health** (NIH).





Summary

- Flavanol/anthocyanin intervention enhances cognitive function, in particular executive function.
- Flavanol/anthocyanin-induced cognitive changes are partially attenuated by pharmacological inhibition of eNOS/nNOS, highlighting a causal role of the vascular system in defining flavonoid actions on cognition.
- Enhancement of cognition, and potentially vascular changes, appear to be partly mediated by increased activity on the ACC following flavonoid supplementation.



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