

# Micronutrients and the brain

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# Vitamins and brain function?

## Mechanisms

## B vitamins are integral to a wide range of brain processes

Membrane potentials (thiamin [B1])

Receptor binding (pyroxidine [B6])

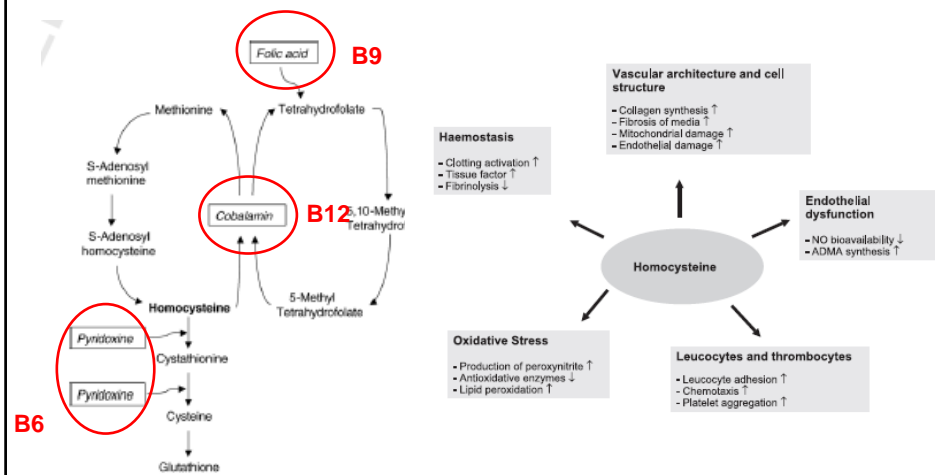
Metabolism of glucose (thiamin, pantothenic acid [B5], riboflavin [B2], nicotinamide [B3])

Physical integrity of neurons (cobalamin [B12], folate [B9])

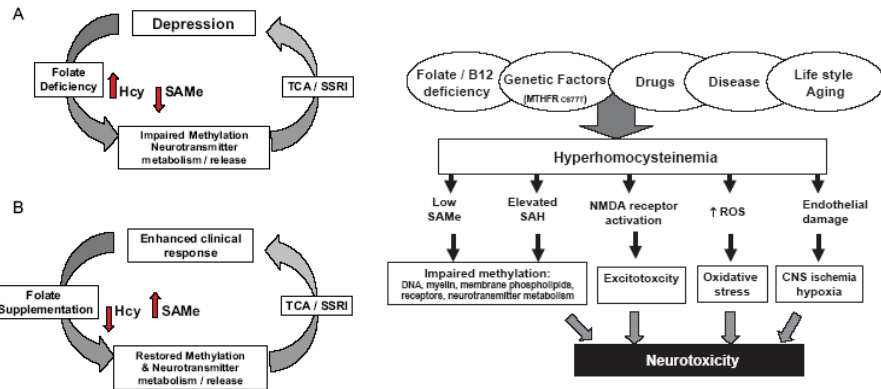
Folate [B9] plays a role in the synthesis and integrity of DNA and the methylation of proteins, phospholipids and neurotransmitters (Mattson and Shea 2003).

Blood supply and metabolism of **homocysteine** [B6, B9, B12]

## Homocysteine



## Homocysteine



## Vitamin D

The active form of Vitamin D (25-hydroxyvitamin D-3) exerts a number of neuroprotective properties, including:

- enhancing endogenous antioxidant defences
- inhibiting inducible nitric oxide synthase
- regulating neuronal calcium homeostasis
- Binds directly to vitamin D receptors in a number of brain regions relevant to cognitive performance (see: Buell and Dawson-Hughes 2008)

## Vitamins and depression - epidemiology

Author and year	Number	Sample	Relationship with B vitamins (+)	Relationship with Homocysteine (-)
Tiemeier et al. 2002	3,884	Elderly	folate, B12	Yes
Morris et al. 2003	2,678	15 - 39 years, 422 depressed	folate	No
Bjelland et al. 2003	5,948	middle aged and elderly	folate (younger women)	Yes
Tolmunen et al. 2004	924	men 46-64 years		Yes

## Vitamins and cognitive performance - epidemiology

Author and year	Number	Sample	Relationship with B vitamins (-)	Relationship with Homocysteine (+)
Feng et al. 2006	451	55-86 years	folate	Yes
Duthie et al. 2002	331	61 - 63 and 76 -78 years	Yes	Yes
Tucker et al. 2005	321	50 - 75 years	Yes	Yes
Kado et al. 2005	499	70 - 79 years		Yes
Elias et al. 2006	812	26 - 98 years	B6	Yes
Vidal et al. 2008	3,914	65+ years	Yes (when tHcy high)	Yes (when folate low)
Elias et al. 2005	2,096	40 - 49, 50 -59, 60 - 82 years		Yes

## Antioxidant vitamins (C and E)

Dietary consumption of the anti-oxidant vitamins (C and E) have also been shown to exert a beneficial effect on cognitive performance (e.g. Paleologos et al 1998, Morris et al 2002), and consumption of both classes of vitamins have been shown to be associated with reduced risk of dementia (for review see: Parigi et al 2006).

## Supplementation?

### **Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people (Review)**

Malouf R, Grimley Evans J

Malouf and Grimley Evans (2008) Cochrane review concludes, on the basis of the 8 studies that met inclusion criteria (all undertaken in elderly or cognitively impaired cohorts) that there was currently no evidence of efficacy for supplementation with folic acid, with or without B vitamin.

### **Vitamin B6 for cognition (Review)**

Malouf R, Grimley Evans J

No good quality trials

## Supplementation?

- Durga et al (2007) well controlled trial in 818 fifty to seventy year old participants selected on the basis of homocysteine levels. They demonstrated that 3 years supplementation with folic acid decreased homocysteine and improved memory, information processing and sensorimotor speed.
- Durga et al (2007) note some that previous studies tended to have small cohorts and use insensitive outcomes such as the Mini Mental State Exam.
- Overall there is a lack of sensitive methodology in the area

## Supplementation?

- 4 relatively small, double blind, placebo controlled trials have investigated adjuvant (to standard psychotropic medication) folate (folic acid or 5-methyltetrahydrofolate) supplementation in depressed patients (Coppen et al 1986, Godfrey et al 1990, Passeri et al 1993, Coppen and Bailey 2000).
- All 4 trials showed some improvements in depression outcomes associated with folate supplementation. Evidence also suggests that folate deficiency is associated with reduced serotonergic and/or neurotransmitter function, and a poorer response to antidepressant medication.

## Supplementation in 'normal', 'healthy' cohorts

### CHILDREN

#### Benton (2001)

- Reviewed the results of studies looking at the effects of vitamins/minerals on IQ test performance in samples of children in the previous decade and noted that performance was improved in ten out of thirteen studies following supplementation, but with this restricted to non-verbal IQ tests.

#### **Cognitive and mood effects in healthy children during 12 weeks' supplementation with multi-vitamin/minerals**

Crystal F. Haskell<sup>1</sup>, Andrew B. Scholey<sup>3</sup>, Philippa A. Jackson<sup>1</sup>, Jade M. Elliott<sup>1</sup>, Margaret A. Defeyter<sup>2</sup>, Joanna Greer<sup>1</sup>, Bernadette C. Robertson<sup>1</sup>, Tom Buchanan<sup>4</sup>, Brian Tiplady<sup>1</sup> and David O. Kennedy<sup>1\*</sup>

Randomised, double-blind, placebo-controlled, parallel groups study.

81 healthy children aged from 8 to 14 years

Computerised internet delivered cognitive assessment on Day 1, 29, 57 and 85

Improved attention task performance across assessments

## Supplementation in 'normal', 'healthy' cohorts

### ADULTS

#### Carroll et al (2000)

- Randomised, placebo-controlled, double-blind study assessing 28 days administration with Berocca, on feelings of stress (Perceived Stress Scale), Anxiety and Depression (HADS) and general health (GHQ-28).
- 80 healthy male participants (18 – 42 years)
- The Berocca group reported **reduced subjective stress** and **decreased anxiety** by the end of the treatment period.

#### Schlebusch et al (2000)

- Randomised, placebo-controlled, double-blind study assessing 30 days administration with Berocca.
- 300 participants suffering high levels of stress
- Improved mood for the Berocca group as assessed on the Hamilton Anxiety Rating Scale (HARS), the Psychological General Well-being Schedule and a stress index

## Study 1 - Berocca and mental performance

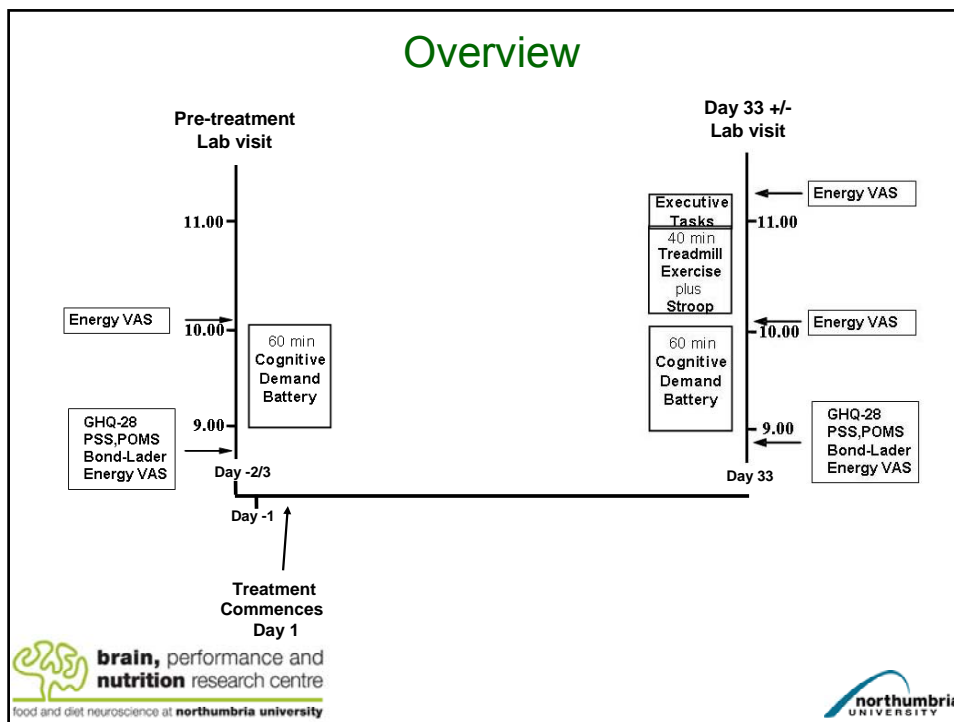
Design: Randomised, placebo-controlled, double-blind study assessing 33 days administration with Berocca.

Outcomes: subjective feelings of stress (Perceived Stress Scale), general health (GHQ), mood (POMS) and mental performance (CDB, Stroop, Executive tasks) .

Participants: 210 healthy male participants (30 – 55 years) in full time work.

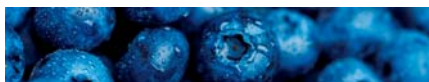
Vitamins:	Amount	Minerals:	Amount
Vitamin B <sub>1</sub>	15 mg	Calcium	100 mg
Vitamin B <sub>2</sub>	15 mg	Magnesium	100 mg
Vitamin B <sub>6</sub>	10 mg	Zinc	10 mg
Vitamin B <sub>12</sub>	10 mcg		
Vitamin C	500 mg		
Biotin	150 mcg		
Folic Acid	400 mcg		
Nicotinamide	50 mg		
Pantothenic acid	25 mg		

## Overview



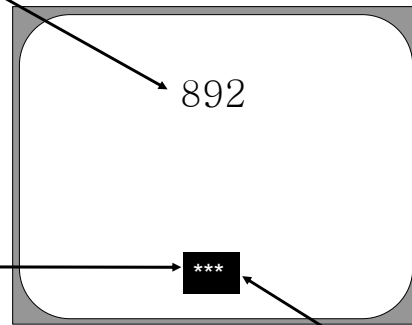
## Cognitive Demand Battery)

- 10 minute battery:
  - Serial threes subtractions (2 mins)
  - Serial sevens subtractions (2 mins)
  - Rapid Visual Information Processing (RVIP – 5 mins)
  - Mental fatigue VAS (1 min)



# Serial subtractions

A random number between 800 – 1000 is generated by the computer as a starting number



Subtract 3 or 7 from that starting number. The response shows as asterisks in the box

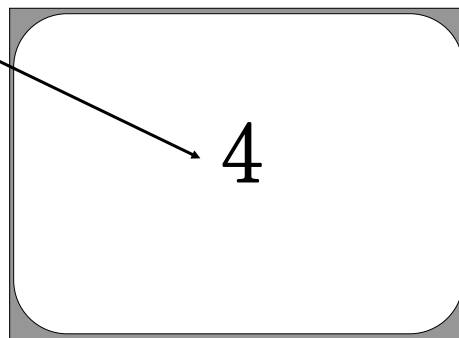
Enter key

Hold this new number in memory



# RVIP

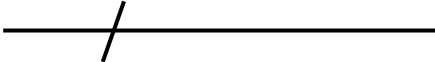
Numbers appear in the middle of the screen at a rate of 100 per minute

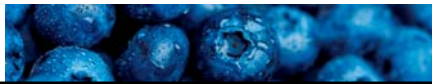


Task is to press the space bar whenever you see three consecutive odd or even digits

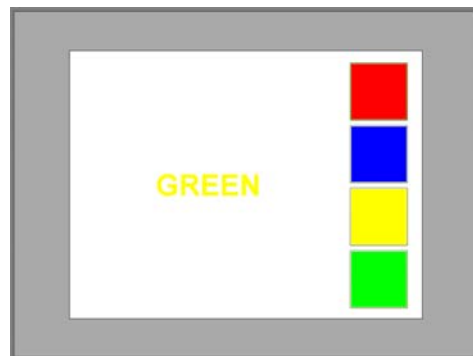


# Mental fatigue

Not at all  Very much so

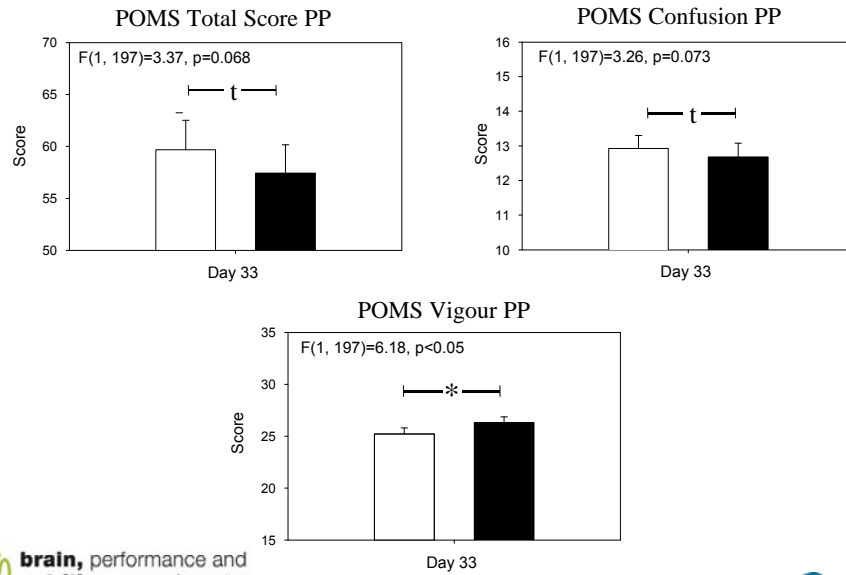


## Executive tasks

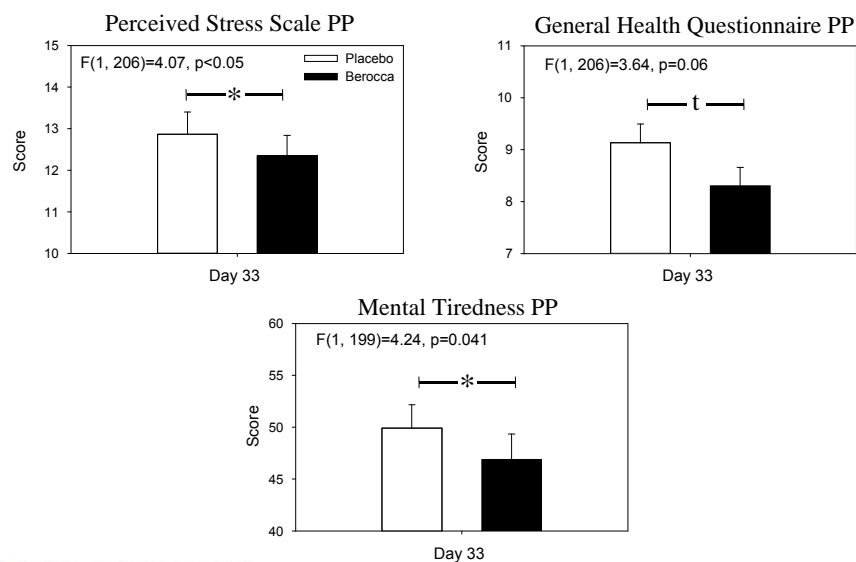


Plus 'Tower of London' and 'Card Sort' executive tasks

## Results



## Results



## Conclusion

Replication of previous findings with regards improved ratings of stress and mood following Berocca

(Carroll et al 2000, Schlebusch et al 2000)

New findings: reduced mental tiredness and improved vigor

## Study 2 - the Effects of Supplementation with Supradyn in Females Self Reporting Fatigue

Design: Randomised, placebo-controlled, double-blind study assessing 9 weeks administration with Supradyn.

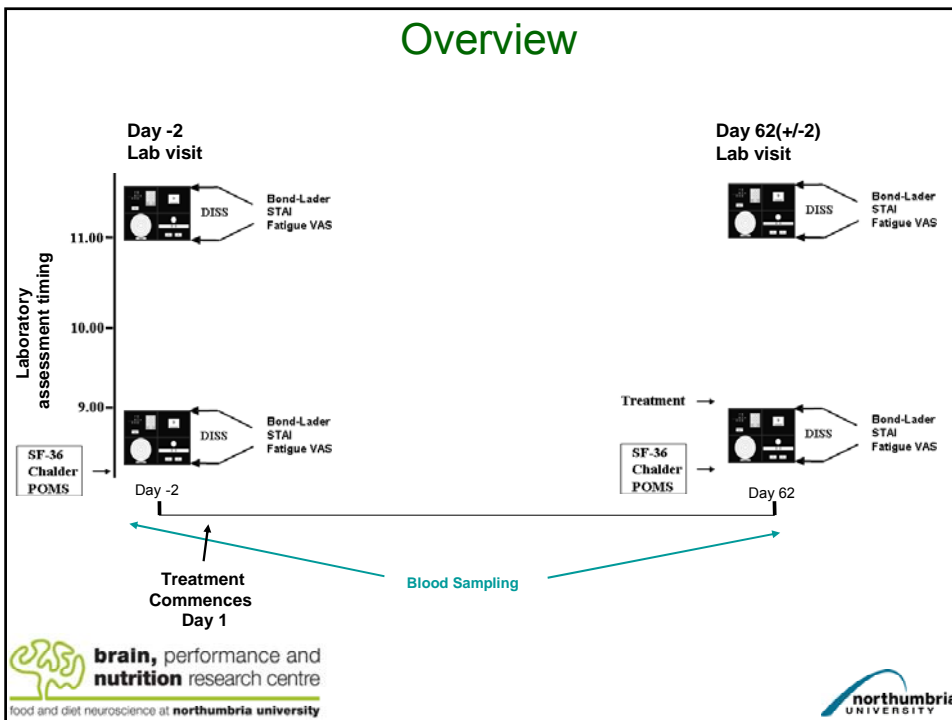
Participants: 220 healthy female participants (25 – 50 years) in full time work or childcare who self-reported fatigue.

Outcomes: Subjective feelings of fatigue (Chalder Fatigue Scale), general health (SF-36), mood (POMS) and performance and the effects of treatment on the negative shift in mood and fatigue inculcated by multi-tasking (Multi-tasking Framework).

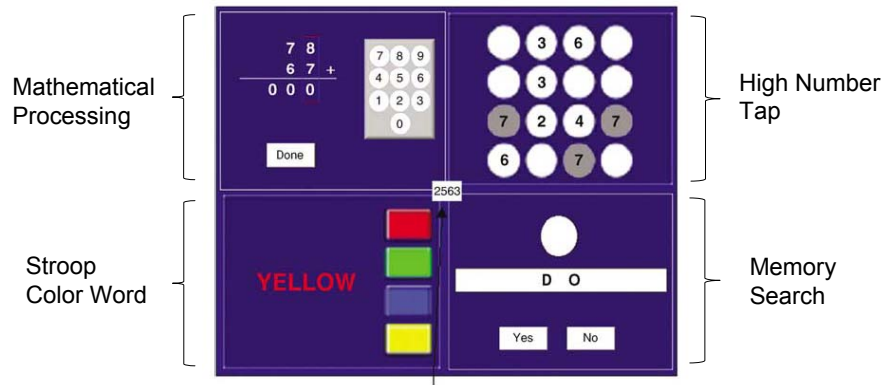
Physiological parameters:  $\alpha$ -amylase, cortisol, Secretory Immunoglobulin A, plasma homocysteine and 8-hydroxy-2'-deoxyguanosine (8-OHdG)

Vitamin A	mg	0.8
Vitamin B <sub>1</sub>	mg	4.2
Vitamin B <sub>2</sub>	mg	4.8
Nicotinamide	mg	54
Pantothenic acid	mg	18
Vitamin B <sub>6</sub>	mg	6
Biotin	mg	0.450
Folic acid	mg	0.6
Vitamin B <sub>12</sub>	mg	0.003
Vitamin C	mg	180
Vitamin D <sub>3</sub>	µg <sup>5</sup>	100
Vitamin E	mg	10
Vitamin K <sub>1</sub>	µg <sup>30</sup>	33
Calcium	mg	120
Phosphorus	mg	126
Chromium	mg	25
Copper	mg	0.9
Fluoride	mg	1.5
Iodine	mg	0.075
Iron	mg	8
Magnesium	mg	45
Manganese	mg	1.8
Molybdenum	mg	0.045
Selenium	mg	0.055
Zinc	mg	8

## Overview



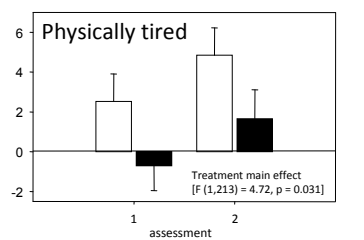
## Multi-tasking Framework



Mood/state assessed before and after multi-tasking with Bond-Lader and mentally/physically tired visual analogue scales.

Reliably shown to inculcate negative shifts in mood and fatigue.

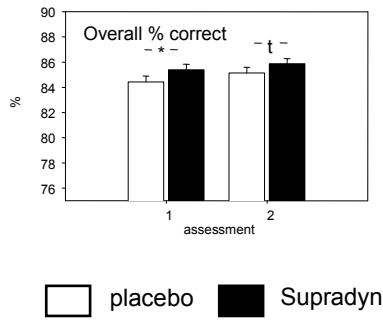
## Effects on negative mood/state inculcated by Multi-tasking



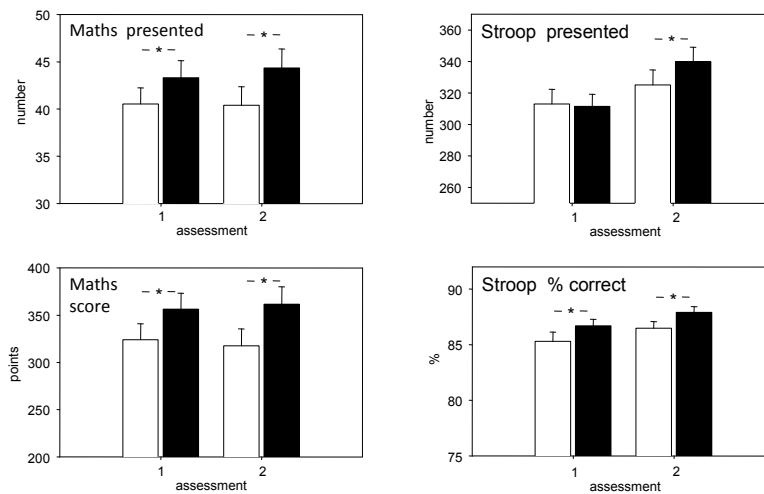
□ placebo    ■ Supradyn

Plus a trend towards improved 'alertness'

## Effects on the ability to multi-task



## Effects on the ability to multi-task

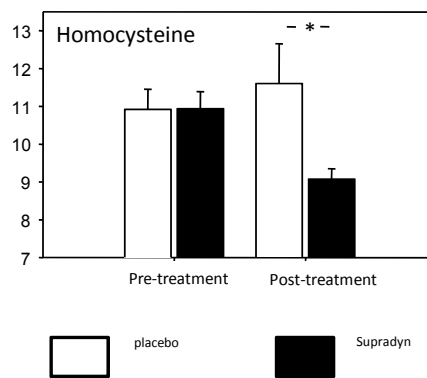


## Physiological parameters

		N =	Pre-treatment		Post-treatment		F	P
Cortisol	placebo	43	0.33	0.17	0.33	0.18	0.02	
	supradyn	50	0.40	0.28	0.35	0.18		
Amylase	placebo	38	51.04	62.42	59.56	71.83	7	0.01*
	supradyn	50	37.09	28.53	26.81	25.73		
SIgA	placebo	40	181.08	152.0	148.4	94.0	1	
	supradyn	49	210.83	128.3	177.6	119.3		
Homocysteine	placebo	44	10.93	3.49	11.60	7.02	8.1	0.006
	supradyn	47	10.94	3.14	9.07	1.91		
8-OHdG	placebo	40	46.90	12.15	46.39	13.13	0.81	
	supradyn	48	46.45	10.11	49.24	15.57		

\*technical difficulty with size of saliva samples.

## Physiological parameters



## Conclusion

Supradyn reduced the negative psychological effects of multi-tasking, specifically attenuating the increase in tiredness caused by the battery, and significantly improved the ability to multi-task.

Homocysteine levels were significantly reduced in this healthy, younger cohort.

## Overall Conclusion

Overall, these findings challenge the assumption that the general population has adequate essential nutrient status and suggest that it may be possible to improve cognitive performance, mood and fatigue/energy simply by increasing micro-nutrient levels, including by direct dietary supplementation.