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Methodology: This study investigated the acute effects of a single multivitamin, mineral and herbal (MVMH) supplement versus placebo on self-ratings of mood and the performance of an effortful computerised cognitive battery in a sample of 76 healthy women aged 50- 75 years. Mood was assessed using the Depression Anxiety Stress Scale (DASS), State Trait Anxiety Inventory – State Anxiety Scale and Visual Analogue Scales (VAS). Mood was rated at one hour post-supplementation and again after the competition of the cognitive assessments at 2 hours post supplementation.

Results: It was demonstrated that the MVMH supplement improved overall DASS mood ratings; however the most prominent effects appeared to be a reduction in ratings of perceived mental stress. These findings were confirmed using Visual Analogue Scales, with these measures also demonstrating MVMH-related increased ratings of calmness. There were no benefits of the MVMH to mood ratings of depression and performance was not enhanced on the cognitive battery.

Conclusions: Supplementation with a single multivitamin, mineral and herbal supplement reduces stress several hours after intake in healthy older people.

Acute mood, but not cognitive improvements following administration of a single multivitamin and mineral supplement in healthy women aged 50 and above: A randomised controlled trial

Macpherson, H*[1,2]., Rowsell, R[1]., Cox, K[1]., Scholey, A[1]., & Pipingas, A[1]

[1]Centre for Human Psychopharmacology
Swinburne University, Melbourne Australia
[2] Centre for Physical Activity and Nutrition Research
Deakin University, Melbourne Australia

* Corresponding author
Email : Helen.macpherson@deakin.edu.au
Ph : +613 9244 5317
Centre for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Faculty of Health
Deakin University
221 Burwood Hwy
Burwood
Victoria 3125
Australia

Disclosures

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Abstract

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Key words: multivitamin; multivitamin/mineral; mood; cognition; stress; elderly

Introduction

A growing literature has indicated that chronic multivitamin supplementation can benefit cognition (Grima et al. 2012) and mood (Long and Benton 2013). Randomised controlled trials have demonstrated that supplementation with multivitamins containing minerals and herbs, over a period of two to four months, can enhance various domains of memory in those over the age of 50 (Harris et al. 2012; Macpherson et al. 2012; Summers et al. 2010). In men aged 50-69 years, eight weeks multivitamin/mineral and herbal (MVMH) supplementation has been shown to reduce symptoms of mood disorder, problems with day-to-day functioning, and increase positive mood experience (Harris et al. 2011). Findings of elevated positive mood associated with chronic multivitamin use has been confirmed in a recent meta-analysis (Long and Benton 2013) which revealed that across eight studies of non-clinical samples, multivitamin supplements improved mild psychiatric symptoms and facets of mood including stress and subclinical anxiety.

Whilst behavioural effects of multivitamins have been generally observed in studies greater than four weeks duration (Grima et al. 2012), very few investigations have focussed on the possibility that multivitamin supplements may influence cognition after a single dose. The first of these studies identified improvements to memory and attention, but not mood, in children aged 8 to 14 years, three hours after the administration of a single multivitamin (Haskell et al. 2008). A more recent study, conducted in healthy adults aged 21- 39 years, utilised brain imaging techniques to investigate the acute effects of multivitamins on neurocognitive function (White et al. 2014). Results from this trial revealed that a single multivitamin, 90 minutes post-dose, increased activation in task-relevant, prefrontal brain regions during the completion of a continuous performance attention task. These findings provide evidence that multivitamins can exert effects on the central nervous system within several hours of ingestion.

Previously, mood benefits of an acute multivitamin dose have only been identified for supplements containing the plant extract guarana, and not for standard multivitamin preparations (Haskell et al. 2008; Kennedy et al. 2008; Scholey et al. 2013). Due to the small number of studies in this area, it is not certain whether these mood effects can be solely attributed to the caffeine content of the guarana extract. Furthermore as these studies are limited to young adults and children, it is not known whether a single multivitamin dose would benefit cognition or mood in older people. We have previously suggested that chronic multivitamin use may be expected to exert greater effects in older people who are at great risk of nutritional deficiency and cognitive decline (Macpherson et al.

2012; Pipingas et al. 2014), but whether the same benefits would be observed following the administration of a single supplement has not been explored in older adults.

The objective of the current study was to explore the mood and cognitive profile of any acute multivitamin effects in women aged 50 to 75 years of age, free from clinical mood disturbances. Secondary results from a four week randomised controlled trial are reported from the acute testing session 1-2 hours following the administration of a single MVMH supplement or placebo. Mood measures were selected which have previously demonstrated sensitivity to multivitamin supplementation over longer time durations (Harris et al. 2011; Long and Benton 2013; Pipingas et al. 2013). Mood ratings were assessed at 1 hour post dose, and again at 2 hours post dose after participants had completed an effortful cognitive battery.

Methods

Study design and treatment

This study adopted a double-blind, placebo-controlled, randomised design. Baseline mood was assessed prior to and after completing a cognitive battery. This procedure was repeated at 1 hour post dose. The MVMH treatment was the Swisse Women's 50+ Ultivite supplement or a placebo matched for appearance and taste. The supplement was administered orally in tablet form. The full ingredients of the Swisse Women's 50+ Ultivite supplement are published elsewhere (Macpherson et al. 2012). In brief the MVMH contains 14 vitamins, 11 minerals, 3 strains of probiotics and 18 herbal extracts. The Swisse Women's 50+ Ultivite supplement contains folic acid, vitamins A, B1, B2, B5, B6, B12, C, E and zinc at levels above the recommended daily intake (RDI). Levels of B3, D3, calcium and magnesium are below the RDI. This study was approved by the Swinburne University Human Research Ethics Committee (SUHREC) and was carried out in accordance with the Declaration of Helsinki. The trial is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12613001087741).

Participants

Participants were 76 women aged 50- 75 years (M = 63.6 years, SD = 6.4 years) who were not engaged in full time employment. All participants were non-smokers, with no history of diabetes, cardiovascular disease, dementia, stroke, other neurological conditions, head trauma, alcohol abuse, clinically diagnosed anxiety, depression, psychiatric disorders, and were not currently using anti-depressant medication, anti-anxiety medication, high dose anti-coagulants, all anti-cholinergic drugs or acetylcholinesterase inhibitors. Participants were required to abstain from supplementation with

vitamin E, multivitamins, B vitamin complex, ginkgo biloba, fish oil, and St John's Wort for 4 weeks preceding the study visit.

Procedure

On the testing day, participants were requested to consume their 'usual' breakfast and to refrain from caffeine consumption. Participants attended the laboratory between 0900 and 1100 hours. All participants signed an informed consent form and completed a medical health questionnaire prior to enrolment in the study. The mini mental state examination (MMSE) (Folstein et al. 1975) and the National Adult Reading Test- Revised (NART-R) (Nelson and Willison 1991) were administered to provide an estimate of global cognitive performance and IQ, respectively. After completing baseline mood and cognitive measures, participants were randomised to receive the MVMH or placebo. Participants were provided with one supplement to take with a glass of water and a slice of wholemeal toast with a choice of two spreads. Following a delay of 1 hour, mood measures were repeated followed by the cognitive battery. Mood measures were repeated a second time after the cognitive measures, corresponding 2 hours post multivitamin dose. The testing procedure is illustrated in Figure 1. The DASS and STAI-S measures were completed using pen and paper versions. The Bond lader and VAS measures were completed using mobile phone devices to enable laboratory and in home assessments (results for longer term supplementation effects and in home assessments presented elsewhere).

Outcomes

All acute outcomes were secondary outcomes from the Behavioural Effects of Multivitamins Supplements (BEMS) study. The primary outcome was mood changes over a longer four week period (details of the four week methodology and findings presented elsewhere).

Mood ratings

Depression Anxiety Stress Scale (DASS) (Lovibond and Lovibond 1995): The DASS is a brief questionnaire comprising 21 items which form *depression*, *anxiety* and *stress* subscales (Lovibond SH 1995). Responses to each item are made on a 4-point scale from 0 to 3, producing a maximal score of 63. Higher scores indicate more symptoms of dysphoric mood, whilst a score of 0 indicates the absence of disturbed mood symptoms. To facilitate the identification of acute mood changes, individuals were required to rate how they were feeling "right now".

State Trait Anxiety Inventory (STAI) – State Anxiety Scale (Speilberger et al. 1969):

The State Anxiety Scale from the STAI consists of 20 items which assesses an individual's current state of anxiety, asking how respondents feel "right now". The State Anxiety Scale assesses intensity of current feelings of stress on a 4-point scale from 1 (not at all) to 4 (very much so). Scores range from 20 to 80 with higher scores indicating greater anxiety.

Bond-Lader Visual Analogue Scale (VAS) (Bond and Lader 1974): The Bond-Lader mood scales require participants to mark the appropriate position on a horizontal line. The scales comprise 16 lines anchored at either end by adjective pairs e.g. happy-sad. Participants are required to mark their current subjective state between the antonyms on the line and each line is scored as the percentage of the total distance from the negative anchor (i.e. higher score indicate more positive mood state). *Three subscales are calculated on the basis of scores from the 16 adjective pairs, representing the factors "alert", "content" and "calm".*

Stress, Anxiety, Concentration, Physical Fatigue and Mental Fatigue Visual Analogue scales (VAS): Each Visual Analogue Scale consists of a single unmarked 100 mm line with end-points labelled 'Not at all' and 'Very much so'. Individuals are instructed to indicate on the line how they feel at that moment in time. Each scale gives a single subjective score between 0 and 100, with lower scores indicative of more desirable mood states on the mood scales and higher energy levels on the fatigue scales. Separate scales were used to assess stress, anxiety, concentration, physical fatigue and mental fatigue.

Cognition

Swinburne University Computerised Cognitive Assessment Battery (SUCCAB)

The SUCCAB stimuli were presented via PC using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) and a hand held button box was used to deliver all responses. Tasks from the SUCCAB have been demonstrated to be sensitive to the effects of chronic MVMH supplementation in older people (Harris et al. 2012; Macpherson et al. 2012). A practice trial was performed immediately prior to each task. An alternate task version was used for the acute 1 hour post treatment time point. The following tasks were undertaken:

Simple reaction time: Speeded response to a white square.

Stroop Congruent: Response to the words RED, YELLOW, GREEN and BLUE presented in the same colour as the written word.

Stroop Incongruent: Response to the words RED, YELLOW, GREEN and BLUE presented in a different colour to the written word. Stroop Interference score was then *c*alculated from *S*troop congruent reaction time subtracted from Stroop incongruent reaction time.

Immediate and delayed recognition memory: Immediate of a series of abstract patterns and delayed recognition at the end of the test battery (30-min delay).

Contextual recognition memory: Recognition of the location of pictures of everyday items presented at one of four locations on the computer screen.

Working memory: The location of 6 white squares in a 4X4 grid was memorised. Participants indicated if squares presented individually were shown in the original array.

Analysis

Baseline group differences on all measures were examined using independent group t tests. Mixed design, analysis of variance (ANOVA) models were used to examine the effects of the MVMH on mood and cognition. To determine whether mood effects were most prominent before or after completing the effortful cognitive assessments, mixed design ANOVAS were conducted for the DASS, STAI and all VAS measures using 2 (Treatment: Multivitamin, Placebo) x 2 (Time: pre-dose, post-dose) x 2 (Task: pre cognitive task performance, post cognitive task performance). On the identification of a significant Treatment x Time interaction, post hoc bonferroni tests were used to examine the difference between baseline and post-treatment measures for each group individually. A series of 2 (Treatment: Multivitamin, Placebo) x 2 (Time: baseline, post treatment) mixed design, repeated measures ANOVAs were used to examine the effects of the MVMH on the cognitive measures. Statistical significance was set at $p < .05$.

Results

Demographics and baseline performance

A total of 39 participants were allocated the multivitamin and 37 allocated placebo. Independent groups t-tests indicated the groups did not differ significantly in terms of age (multivitamin M = 64.4, placebo M = 62.8, $p = .28$) or MMSE score (multivitamin M = 29.3, placebo M = 29.4, $p = .75$). The multivitamin group had completed significantly greater years of education (multivitamin M = 17.0, placebo M = 15.4, $p = .03$) and had a higher NART IQ score (multivitamin M = 119, placebo M = 116, $p = .02$). The most commonly reported medications were cardiac medications (multivitamin n = 13, placebo n = 10) and arthritis medications (multivitamin n = 3, placebo n = 4). Independent groups t-tests indicated there were no significant baseline differences between the multivitamin and placebo groups on any of the mood or SUCCAB outcome measures. Mean correct was over 95% for the simple reaction time and stroop measures indicating these tasks were performed at ceiling,

therefore only response time was examined as an outcome for these tasks. A log transformation was applied to the DASS total score, anxiety and depression subscale scores to correct for a positive skew. Means and standard deviations for each measure are shown in Table 1 and Table 2.

Acute mood effects of the multivitamin

Depression Anxiety Stress Scale: A significant Time x Treatment interaction for the DASS total score was identified (F (1,72) = 5.54, p = .02, η^2 = 0.07). Post hoc bonferroni tests indicated there was a significant reduction in DASS score for the multivitamin group only (p < .001). A significant Time x Treatment interaction for the DASS stress score was identified (F (1,72) = 6.97, p = .01, η^2 = 0.09). Post hoc bonferroni tests indicated there was a significant reduction in DASS score for the multivitamin group only (p <.001). Change from baseline DASS scores are shown in Figure 2 to demonstrate the magnitude of these changes.

Visual Analogue Scales: A significant Time x Treatment interaction for the Bond Lader VAS calmness score was identified (F (1,71) = 5.37, p = .02, η^2 = 0.07). Post hoc bonferroni tests indicated there was a significant increase in calmness for the multivitamin group only (p = .003). A significant Time x Treatment interaction for the VAS stress score was identified (F (1,71) = 7.44, p = .008, η^2 = 0.10). Post hoc bonferroni tests indicated there was a significant reduction in VAS stress rating for the multivitamin group only (p = .001). A significant Time x Treatment interaction for the VAS anxiety score was identified (F (1,71) = 4.38, p = .04, η^2 = 0.06). Post hoc bonferroni tests indicated the reduction in VAS anxiety did not reach statistical significance for either group.

Controlling for group differences in years of education and NART-IQ did not alter the statistical significance of any mood ratings, with the exception of the VAS rating of anxiety which was diminished to a trend following adjustment for baseline differences in IQ (1,69) = 3.24, p = .08, η^2 =.05). Main effects of Time are shown in Table 2. There were no significant main effects of Treatment identified for any mood measures.

Effects of the cognitive battery on mood ratings

As shown in Table 2, a significant main effect of Task was identified for a number of VAS ratings, indicating that participants reported a reduction in alertness, contentedness, calmness, higher levels of stress, anxiety, greater mental fatigue, physical fatigue and reduced concentration after completing the cognitive battery.

Acute cognitive effects of the multivitamin

There were no significant Time x Treatment interactions for the cognitive measures. As shown in Table 2, a performance on a number of SUCCAB measures improved significantly from baseline to post-treatment, regardless of which treatment was administered. There were no other significant main effects identified for the SUCCAB measures. Controlling for group differences in years of education and NART-IQ did not alter the statistical significance of any cognitive measures.

Discussion

The results of the present study indicated that MVMH supplementation can benefit mood 1-2 hours post dose. Specifically, it was found that taking a single multivitamin improved overall mood ratings on the DASS and this effect appeared to be driven by a significant reduction in stress ratings. The MVMH was associated with decreased ratings of stress and increased ratings of calmness on the visual analogue scales. There were no benefits to aspects of mood including depression or ratings of physical and mental fatigue at any time point. In contrast to chronic studies in older people, which have shown improvements to memory (Harris et al. 2012; Macpherson et al. 2012; Summers et al. 2010), a single MVMH dose did not exert any effects on cognitive performance.

The potential for a single multivitamin dose to modulate mood and cognition has not previously been investigated in an older sample. Similar to a four week study in men of a comparable age range (Harris et al. 2011), the current study identified improvements on the overall DASS score following MVMH administration. In this study, the acute mood benefits were most apparent on ratings of perceived stress, with two measures of stress and a measure of calmness and anxiety all showing an improvement following the MVMH dose. However, it must be noted that the effect of the multivitamin on anxiety was attenuated when controlling for baseline group differences in IQ. Relative to assessments taken both before, and after completing the effortful cognitive assessments, the MVMH reduced DASS stress score by over 30%. By contrast, stress reductions attributed to the placebo were in the order of 11% and less. Interestingly, stress is the mood facet which has also been reported to show the greatest improvements following chronic multivitamin supplementation (Long and Benton 2013). Benefits to stress ratings following ≤ one month of multivitamins containing high dose vitamin B have been observed in non-clinical samples in a number of randomised controlled trials (Carroll et al. 2000; Kennedy et al. 2010; Schlebusch et al. 2000; Stough et al. 2011). Whilst lower dose B vitamin supplements have been associated with both positive (Harris et al. 2011) and negative findings (Haskell et al. 2010).

Mood benefits of chronic multivitamin supplementation have largely been attributed to folate, B6 and B12, which have important roles in neurotransmitter synthesis (serotonin, noradrenaline and

dopamine) (Huskisson et al. 2007), and in the remethylation of homocysteine to SAMe (Bottiglieri 2005). For instance, B12 and folate deficiencies have been associated with higher levels of depression (Alpert et al. 2000; Baldewicz et al. 2000; Tolmunen et al. 2003). The potential of folate in the reduction of clinical mood states is well documented (Bottiglieri 2005), and may also have an effect in non-clinical populations (Malouf et al. 2003). Additionally, poorer mood has been associated with lower levels of vitamin D, zinc and selenium (Benton 2002; Levenson 2006; Wilkins et al. 2006). Thiamine and the minerals calcium, magnesium and iron have also been postulated to influence mood through a number of biological pathways (Kaplan et al. 2007).

To date, the mechanism regarding acute effects of multivitamin supplementation on mood is unexplored in the literature. Some have suggested that improved vascular endothelial function and improvements in mitochondrial function as a potential mechanism for acute cognitive improvements (Kennedy et al. 2008). For instance, improved vasodilation and blood flow to the brain, results in the increased delivery of metabolites to active tissue, leading to improved task performance (Scholey et al. 2001). Without the measurement of blood metabolites in this study, potential mechanisms can only be speculated. Bioavailability data has demonstrated that when taken in tablet form, 1000 µg of folic acid leads to peak serum folate levels two hours after ingestion, with levels approaching the peak even at one hour post dose (Maki et al. 2012). A lower level of 500µg folic acid was included in the MVMH treatment examined in the current study, however the timeframe for mood benefits appears to be consistent with the peak folate concentration described by Maki et al. (2012).

In the current study we examined whether any mood effects were strongest following the completion of an effortful cognitive battery, which was demonstrated to increase anxiety, stress, mental fatigue and physical fatigue, whilst reducing alertness, calmness and concentration. Acute psychological stressors, even for short durations can induce cardiovascular, digestive, and immune system changes and increase circulating levels of the hormone cortisol, due to activation of the hypothalamic-pituitary-adrenal (HPA) axis (Kemeny 2003). It has also been suggested that psychological stress impairs methylation reactions, resulting in alterations to the availability of nutrients for neurotransmitter synthesis and function (Kaplan et al. 2007). Given the MVMH contained a range of B vitamins (including vitamin B6, B12 and folate at levels equivalent to the recommended daily intake) it may have been anticipated that any stress induced by the cognitive assessments would be offset by the supplement. Instead, the results provided evidence of a general reduction to stress levels which were not indicative of protection against short term increases to stress levels. A limitation of this study was that mood assessments were only taken 1 and 2 hours post dose therefore it is not known how long any benefits were sustained.

It is not clear why mood, but not cognitive benefits were observed in this study, as cognitive improvements and brain functional changes have been identified several hours after a single multivitamin dose in younger participant groups (Haskell et al. 2008; White et al. 2014). The same working memory (Macpherson et al. 2012) and episodic memory measures (Harris et al. 2012) used in the current study have previously demonstrated benefits following two to four months MVMH supplementation, indicating the assessments used in this study were suitable to detect improvements due to multivitamin supplementation. It may be that in an older sample, who are more prone to nutritional insufficiencies (Brownie 2006), our previously reported cognitive benefits of multivitamins (Harris et al. 2012; Macpherson et al. 2012) are due to a cumulative effect of improving nutritional status over time. More studies are required across both males and females to confirm or negate this premise, particularly as the current study solely focussed on women, and cannot confirm whether males would demonstrate the same acute response following multivitamin intake. A final note of consideration is that some chronic studies which have identified mood benefits of multivitamins have not reported whether participants consumed the supplement on the day of post-treatment testing (Carroll et al. 2000; Kennedy et al. 2010; Stough et al. 2011). This gives rise to the possibility that the stress reductions reported in these trials may be due to acute effects of multivitamins, if participants did not abstain from supplementation on the day of post-treatment assessments. Findings from the current study suggest that mood may be elevated for several hours following multivitamin intake. Therefore the timing of supplement intake may be an important methodological consideration when comparing results across different trials.

In summary, findings from this study indicate that there are acute mood, but not cognitive effects of multivitamin supplements. Specifically, in healthy older women a single multivitamin, mineral and herbal dose may lead to general mood enhancements, predominantly by reducing stress levels.

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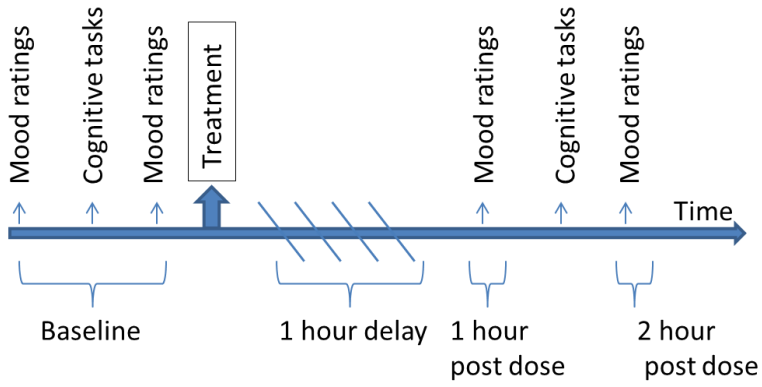

Figure 1. Timing of tasks and treatment

Table 1. Mean and standard deviations (SD) for the mood assessments, with *p* values shown for the Main Effects of Task (pre and post battery) and Time (pre and post dose) and Time x Treatment Interaction.

Mood Measure	Treatment Group	N	Baseline Mean (SD)	Post Dose Mean (SD)	Time *p*	Task *p*	Interaction *p*
DASS							
Total (pre battery)	Multivitamin	38	10.4 (12.2)	6.7 (9.9)	<.001***	.13	**.02***
	Placebo	36	7.6 (9.9)	6.4 (8.5)			
Total (post battery)	Multivitamin	38	10.1 (10.6)	6.7 (8.8)			
	Placebo	36	8.3 (9.9)	7.4 (10.7)			
Depression (pre battery)	Multivitamin	38	2.4 (4.3)	1.6 (3.2)	.002**	.50	.32
	Placebo	36	1.6 (3.5)	1.2 (3.1)			
Depression (post battery)	Multivitamin	38	2.0 (3.8)	1.1 (2.7)			
	Placebo	36	1.7 (3.5)	1.6 (4.4)			
Anxiety (pre battery)	Multivitamin	38	2.1 (3.5)	1.3 (2.3)	.02*	.97	.23
	Placebo	36	1.5 (2.7)	1.3 (1.9)			
Anxiety (post battery)	Multivitamin	38	1.8 (2.4)	1.4 (2.6)			
	Placebo	36	1.9 (2.9)	1.2 (2.2)			
Stress (pre battery)	Multivitamin	38	5.8 (5.8)	3.8 (5.3)	<.001***	.06	**.01***
	Placebo	36	4.4 (5.0)	3.9 (5.3)			
Stress (post battery)	Multivitamin	38	6.3 (5.9)	4.2 (5.1)			
	Placebo	36	4.7 (5.0)	4.6 (5.5)			
VAS							
Alert (pre battery)	Multivitamin	37	68.1 (18.0)	68.2 (19.0)	.14	<.001***	.31
	Placebo	36	72.5 (15.3)	71.5 (17.4)			
Alert (post battery)	Multivitamin	37	57.7 (18.0)	56.5 (18.1)			
	Placebo	36	61.0 (15.6)	56.6 (15.9)			
Content (pre battery)	Multivitamin	37	77.1 (17.3)	78.8 (15.1)	.98	<.001***	.11
	Placebo	36	83.0 (14.5)	83.5 (16.3)			
Content (post battery)	Multivitamin	37	64.9 (17.3)	66.0 (16.1)			
	Placebo	36	72.5 (16.4)	69.2 (15.8)			
Calm (pre battery)	Multivitamin	37	66.5 (21.7)	74.3 (17.4)	**.**04*	<.001***	**.02***
	Placebo	36	75.9(17.5)	75.6 (23.3)			
Calm (post battery)	Multivitamin	37	55.6 (19.1)	59.7 (19.1)			
	Placebo	36	63.5 (20.9)	63.2 (18.2)			
Stress (pre battery)	Multivitamin	37	23.9 (24.4)	15.4 (17.9)	.06	<.001***	.**008****
	Placebo	36	14.3 (17.7)	15.1 (20.3)			
Stress (post battery)	Multivitamin	37	43.7 (23.7)	35.9 (17.9)			
	Placebo	36	34.2 (23.8)	36.2 (23.6)			
Anxiety (pre battery)	Multivitamin	37	18.2 (22.1)	14.1 (14.5)	.95	<.001***	**.04***
	Placebo	36	13.9 (19.1)	15.9 (22.3)			
Anxiety (post battery)	Multivitamin	37	31.5 (22.1)	29.4 (16.0)			
	Placebo	36	29.4 (20.9)	33.2 (23.3)			
Concentration (pre battery)	Multivitamin	37	65.7 (29.0)	59.8 (26.1)	.19	<.001***	.83
	Placebo	36	63.8 (26.7)	60.8 (27.1)			
Concentration (post battery)	Multivitamin	37	54.7 (25.6)	53.6 (21.2)			
	Placebo	36	56.9 (20.9)	54.9 (19.9)			
Mental Fatigue (pre battery)	Multivitamin	38	23.1 (24.0)	30.3 (24.3)	.003**	<.001***	.97
	Placebo	36	22.4 (22.0)	27.1 (23.6)			
Mental Fatigue (post battery)	Multivitamin	38	43.4 (23.7)	48.3 (20.4)			
	Placebo	36	41.9 (21.0)	49.1 (20.5)			
Physical Fatigue (pre	Multivitamin	37	21.3 (23.3)	27.0 (23.4)	.01*	<.001***	.35

battery)	Placebo	36	16.7 (18.9)	22.6 (20.2)			
Physical Fatigue (post	Multivitamin	37	36.4 (22.7)	35.5 (20.7)			
battery)	Placebo	36	27.7 (16.8)	32.0 (19.3)			
STAI - S							
STAI (pre battery)	Multivitamin	39	33.2 (10.8)	30.3 (8.0)	.001**	<.001***	.24
	Placebo	36	30.5 (9.0)	28.7 (9.5)			
STAI (post battery)	Multivitamin	39	35.5 (11.4)	32.6 (9.4)			
	Placebo	36	32.6 (12.0)	31.4 (9.9)			

DASS = Depression Anxiety Stress Scale
VAS = Visual Analouge Scale
STAI - S = State trait anxiety inventory - State
Bold font indicates a significant Time x Treatment interaction * p <.05 level, ** p <.01 level, *** p<.001 level

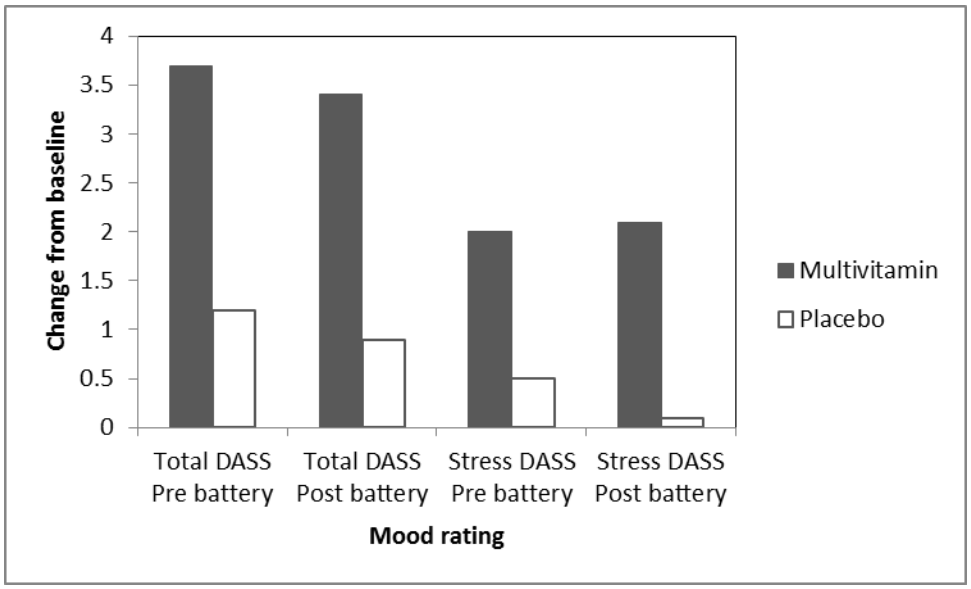

Figure 2. Change from baseline scores for the Depression Anxiety Stress Scale (DASS) total score and DASS stress subscale for mood ratings prior to, and after performance of the effortful cognitive battery

Table 2. Mean and standard deviations (SD) for the cognitive assessments, with *p* values shown for the Main Effect of Time (pre and post dose) and the Time x Treatment Interaction

SUCCAB Task	Treatment Group	N	Baseline Mean (SD)	Post Dose Mean (SD)	Time *p*	Interaction *p*
Simple Reaction rt	Multivitamin	37	320 (107)	332 (104)	.94	0.38
	Placebo	36	311 (82)	301 (35)		
Stroop Congruent rt	Multivitamin	39	795 (114)	759 (124)	<.001***	0.97
	Placebo	37	766(109)	731 (102)		
Stroop Incongruent rt	Multivitamin	37	898 (131)	909 (146)	.29	0.99
	Placebo	35	877 (108)	889 (123)		
Stroop Interference rt	Multivitamin	37	104 (69)	152 (82)	<.001***	0.40
	Placebo	34	118 (100)	149 (89)		
Contextual Recognition rt	Multivitamin	35	1019 (97)	1022 (94)	.39	0.58

	Placebo	36	995 (106)	1013 (121)		
Contextual Recognition %	Multivitamin	35	79.3 (14.1)	81.6 (12.1)	.23	0.98
	Placebo	35	77.1 (15.1)	79.4 (13.1)		
Immediate Recognition rt	Multivitamin	39	1015 (111)	1014 (115)	.04*	0.06
	Placebo	35	1036 (136)	990 (112)		
Immediate Recognition %	Multivitamin	39	71.0 (12.9)	76.7 (11.0)	<.001***	0.71
	Placebo	35	70.8 (12.1)	77.6 (12.1)		
Delayed Recognition rt	Multivitamin	37	1017 (86)	1009 (114)	.24	0.64
	Placebo	36	1000 (88)	982 (106)		
Delayed Recognition %	Multivitamin	37	69.4 (14.3)	73.6 (12.4)	.01*	0.56
	Placebo	36	70.5 (10.6)	73.0 (12.4)		
Working Memory rt	Multivitamin	39	1056 (147)	1020 (154)	.03*	0.70
	Placebo	36	1029 (131)	994 (125)		
Working Memory %	Multivitamin	39	69.8 (15.0)	72.8 (14.3)	.01**	0.58
	Placebo	37	67.3 (15.6)	72.0 (13.0)		

* p <.05 level, ** p <.01 level, *** p<.001 level