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A Randomized Double-Blind Placebo-Controlled Trial of a Purported Dietary Supplement Cognitive Enhancer in Healthy Teenage Subjects

Original Research

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Abstract

Introduction: The prevalence of using dietary supplements among teenagers is rising. In particular, the use of nutritional supplements to improve cognitive performance is becoming more commonplace. Given the prevalence of use, it is important to empirically assess the effects of nutritional supplements on cognitive performance. The current study sought to test the effects of an existing cognition supplement, Brain Doctors' Formula® (BDF) Mega Brain Boost® (MBB), across different cognitive domains in a healthy teenage population.

Methods: We carried out a 6-week randomized, placebo-controlled, double-blind study. The study lasted approximately 42 days (6 weeks) for each participant. Study visits included screening and baseline testing, week 3 interim and week 6 end of study visit. Cognition outcomes were measured by the National Institutes of Health (NIH) Toolbox Cognitive Battery of Testing (Dimensional Change, Flanker, and Pattern Comparison) and a Symmetry Span Task at baseline, interim, and final visits. Another efficacy outcome was the self-assessment of mind wandering, which was captured in a study daily diary from baseline to the end of study visit. There were two study groups, including one MBB group and one placebo group. Twenty-four participants were screened and randomized to include 12 participants in each group.

Results: The change from baseline to interim (Week 3) and from baseline to the final visit (Week 6) did not show a significant between-group difference on any measure of cognition (all p-values >0.05) except one. There was a significant between-group difference with a large effect size at Week 3 showing that the MBB group performed significantly better than the placebo group on the Dimensional Change Card Sort Task.

Conclusions: This study suggests that MBB potentially improves executive cognitive processes (as assessed by the Dimensional Change Card Sort Task) in healthy teenagers. However, this effect was only significant at the interim visit. Therefore, it is uncertain if there are any lasting beneficial effects. Further research should be conducted in a larger group of participants and focus on broader measures of executive function.

Key Words: alpha-GPC, Cognition, Nootropics, Phosphatidylserine, Pyrroloquinoline Quinone, Spearmint

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Introduction

Treatment to improve cognitive performance among teenagers is increasing in popularity and use [1-4]. However, cognitive boosting supplements, also known as "nootropics" show mixed/limited benefits or negative side effects [5-7]. Therefore, it is critical to test nutritional supplements for their efficacy in improving cognitive processes such as attention, perception, evaluation, and working memory.

As with the general population, the prevalence of using dietary supplements among teenagers has also been rising recently. A national survey by the Centers for Disease Control and Prevention (CDC) found that about 1/3 of children and adolescents in America use dietary supplements in their everyday life and teenagers' (between 12 – 19 years old) use of two or more dietary supplements showed an overall increase between the year of 2009 – 2018 [4]. In addition, the use of mineral and herbal supplements in teenagers is associated with a decrease in weight and body fat, and an increase in the number of team sports an adolescent played [8]. Herbal supplements also show benefits in improving a person's cognitive function; for example, use of soy-derived phosphatidylserine (PS) led to improvements in symptoms of attention-deficit hyperactivity disorder (ADHD), short-term auditory memory, and working memory in children between age 4 – 14 [9].

Previous literature has indicated that spearmint extract may have anti-oxidative and anti-inflammatory effects [10]. Faccone et al. performed a study on 142 volunteers and reported a significant improvement in sustained attention after taking 900 mg of spearmint extract daily for 90 days, compared to placebo [11].

PS is a phospholipid found abundantly in the brain that has also been shown to be effective in improving cognition [12]. A pilot study conducted by Moré *et al.* on elderly Alzheimer's Disease and dementia participants reported positive effects on memory, mood, and cognition after consuming a supplement blend of 100 mg PS and 80 mg phosphatidic acid for 3 months when compared to a placebo group [13].

Alpha-Glyceryl Phosphoryl Choline (alpha-GPC) is a water-soluble phospholipid that has anti-inflammatory and antioxidative properties. Literature suggests that alpha-GPC may increase levels of acetylcholine—a neurotransmitter that plays a major role in cognitive and motor function [14 15]. Further, pyrroloquinoline quinone (PQQ) has been demonstrated to have antioxidative effects and promotes the generation of new mitochondria [16]. However, literature on the beneficial effect of this ingredient is limited to adult populations [17].

Therefore, this study was conducted to determine whether the nutritional supplement, Brain Doctors' Formula® (BDF) Mega Brain Boost® (MBB) containing the active ingredients spearmint extract, PS, alpha-GPC, and PQQ, was effective in improving cognitive function in healthy teenagers. To answer this question, we carried out a 6-week randomized, placebo-controlled, double-blind study to assess the effects of MBB on multiple measures of cognition in 24 healthy volunteers aged 12 to 18 years using a series of tests from the National Institutes of Health (NIH) Toolbox, A Symmetry Span task, as well as a self-report measurement of cognition functioning.

Scientific Methods

This was a randomized, placebo-controlled, double-blind study to assess the effects of MBB (provided by Besten Corporation, Irwindale, CA, USA) on multiple measures of cognition in healthy teenagers.

Participants

There were two study groups, including one Mega Brain Boost® (MBB) group and one placebo group. Twenty-four (24) participants were screened and randomized for the study; however, two participants withdrew from the study after one week of supplementation, leaving 10 participants in the MBB group and 12 participants in the placebo group completing the study. The mean age of participants was 15.7±2.08 years old. There was not a significant difference in age between the placebo (mean = 15.5±2.15) and the test product group (mean = 15.9±2.08) [$t(20) = 0.44$, $p = 0.33$]. There were 15 males in the study. All procedures were carried out in accordance with a protocol reviewed and approved by the Nova Southeastern University Institutional Review Board. Three consent forms were used for this study. One assent for participants who were 12 years old, one consent form for participants who were 13-17 years old, and one consent form for participant who were 18 years old. A researcher reviewed the consent form and study procedures with all participants and their legal guardians (for those under 18 years of age) prior to signing the consent forms.

Protocol

The study lasted approximately 42 days (6 weeks) for each participant. The study included a screening visit, which was on the same day as the baseline visit for all participants. Participants who completed the screening process and qualified to continue were randomized to receive either MBB or placebo in a 1:1 ratio. They were assigned a unique randomization code at the baseline visit on Day 0. Participants consumed the assigned study product for 42 days (6 weeks) with an interim visit on Day 21 ± 2, followed by an end of study/final visit on Day 42 ± 2. The study included a total of three in-person visit days: screening/baseline, interim, and final visit. Efficacy outcomes include the NIH Toolbox Cognitive Battery of Testing [Dimensional Change Card Task (DCCST), Flanker Inhibitory Control and Attention Task (Flanker Task), and Pattern Comparison Speed of Processing Task (PC Task)] and Symmetry Span (SS) Task which were assessed at baseline, interim, and final visits. Another efficacy outcome was the self-assessment of daily mind wandering, which was captured in a study daily diary from baseline to the end of study visit.

Supplementation

Participants were randomized in a 1:1 ratio to either MBB or placebo. Participants were expected to consume two tablets orally each day with water around the same time every day, ideally after a meal for 6 weeks. If a dose was missed, participants were instructed to take it as soon as it was realized on the same day and then return to the scheduled dosing time. Subjects were instructed not to make up a dose if missed one.

Screening Measures

During the screening, each participant underwent a review of medical history, and a review of concomitant medications and therapies, and dietary supplements. Their body anthropometrics were measured via an InBody H20B (InBody USA, Cerritos CA). Heart rate and blood pressure were also measured. Finally, participants completed a cognition screening measure using the Brief Child and Family Phone Interview (BCFPI) Questionnaire. BCFPI has 11 scales (for ages 12-18 years) to assess externalizing behavior, internalizing behavior, state/sense regulation as well as an overall total score for cognitive ability. This questionnaire was used to screen for any potential social/emotional issues. No participants were screen-failed; all participants were subsequently randomized into the study following the screening. There were no significant between-group differences in screening measures (see Tables 1 and 2).

Table 1 Body Composition Measures

	Placebo (n = 12)	**MBB (n = 10)**
Height (cm)	170.39± 10.91	170.18± 12.84
Weight (kg)	63.52± 19.77	61.18± 11.78
SMM* (lbs)	57.82± 16.66	57.14± 17.76
Body Fat (%)	23.21± 10.43	23.82± 11.69
BMI*	21.52± 5.41	21.06± 2.75

Data are presented as Means ± SD

*SMM = Skeletal Muscle Mass, BMI = Body Mass Index

Table 2. BCFPI scores*

	Placebo (n = 12)	**MBB (n = 10)**
ITEM 1: Attention/Impulsivity	3.58 ± 2.11	3.70 ± 1.16
ITEM 2: Oppositional Behavior	2.00 ± 1.65	2.20 ± 1.87
ITEM 3: Conduct Problems	0.17 ± 0.58	0.10 ± 0.32
ITEM 4: Separation Anxiety	2.08 ± 2.02	2.20 ± 2.10
ITEM 5: Managing Anxiety	4.50 ± 1.98	5.10 ± 1.73
ITEM 6: Managing Mood	1.75 ± 2.22	1.50 ± 1.84

Data are presented as Means ± SD

On the BCFPI higher score indicates poorer self-reported functioning for each item. Item 1: The questions in this section relate to regulation of attention, impulsivity, and activity. A score of 10 or above is considered elevated. Item 2: The questions in this section relate to oppositional/co-operative behavior in relationships. A score of 11 or above is considered elevated. Item 3: The questions in this section relate to conduct problems. A score of 4 or above is considered elevated. Item 4: The questions in this section relate to separation anxiety. A score of 7 or above is considered elevated. Item 5: The questions in this section relate to managing anxiety. A score of 8 or above is

considered elevated. Item 6: The questions in this section relate to managing mood. A score of 9 or above is considered elevated.

Cognition Measures

Cognition was measured via a battery of tests from the NIH toolbox and a Symmetry Span task. The NIH toolbox measures provide an age-corrected standard (T) score. This score corrects the score of the test-taker by accounting for age based on normative data. The NIH cognitive battery of testing includes a series of validated assessments, some of which can test the participant's executive function, attention, and processing speed [18 19]. This study included the Dimension Change Card Test, the Flanker Inhibitory Control and Attention Test, and the Pattern Comparison Speed Test completed at baseline, Week 3, and Week 6. The Dimension Change Card Test is a method of assessing executive function in adolescents by sorting test cards by either color or shape. The Flanker Inhibitory Control and Attention Test assesses the participant's attention and inhibitory control by indicating the direction of a central stimulus among distractor stimuli (i.e., identifying which way the middle arrow is pointing in a row of similarly looking arrows). The Pattern Comparison Speed Test evaluates the participant's processing speed by identifying (yes/no) whether two images are the same.

The Symmetry Span Task was used to assess working memory capacity. The Symmetry Span Task gives a raw performance score and therefore there is no age-correction for this measure. The task is to remember the location of a series of red squares on a white 4 x 4 square grid presented during a concurrent processing task requiring participants to determine whether another image being shown is symmetrical on its vertical axis [20]. Following the series of between 2-5 to be remembered square and symmetry verification pairs, participants were asked to recall the location of the red squares in the order presented.

Participants also filled out a daily study diary that served two purposes. The first was to capture self-reported daily study product consumption (i.e., date, time of study product consumption, and any missed doses). The second purpose was to capture self-reported mind-wandering through a series of self-reported questions.

Statistical Analysis

All calculations and analyses were performed using IBM SPSS Statistics version 28.0.1. Outliers on individual tasks were identified and removed using the interquartile range (IQR) [21]. The change from baseline was compared between the groups (MBB vs. Placebo) via independent samples t tests for cognition tasks. The daily diary measures were compared between groups at each week via independent samples t tests for mind wandering. Blood pressure and heart rate were analyzed via a 2 X 3 (Group x Time) repeated measures ANOVA. The significance level was set at alpha= 0.05.

Results

A series of independent samples t tests on change scores from baseline to interim (Week 3) and from baseline to the final visit (Week 6) did not show a significant between-group difference on any measure (all p-values > 0.05) except one. There was a significant difference at Week 3 showing that the MBB group exhibited a significantly better change from baseline than the placebo group on the Dimensional Change Card Sort Task [t(19) = 1.88, p = 0.038, d = .82].

Table 3. Changes from baseline in Cognition Measures

		Placebo			MBB		
		n	Mean	SD	n	Mean	SD
Week 3	**Flanker**	12	3.42	5.21	9	5.33	6.00
	Dimensional Change	11	-2.45	7.63	10	3.50*****	6.80
	Pattern Comparison	11	11.09	17.96	10	14.40	9.69
	Symmetry Span	11	0.73	3.95	10	1.50	2.64
Week 6	**Flanker**	12	6.83	12.95	9	5.22	5.76
	Dimensional Change	12	0.25	17.25	10	6.60	11.10
	Pattern Comparison	11	23.09	19.09	10	16.30	13.98
	Symmetry Span	11	1.27	4.24	10	1.2	4.08

NIH Toolbox measures (Flanker, Dimensional change, and Pattern Comparison) were evaluated using age-corrected T-scores. Week 3 data represent the change from baseline to the interim visit, where a significant between-group difference (p = 0.038) was observed. Week 6 data represent the change from the baseline to the final visit, and there was not a significant difference between the groups.

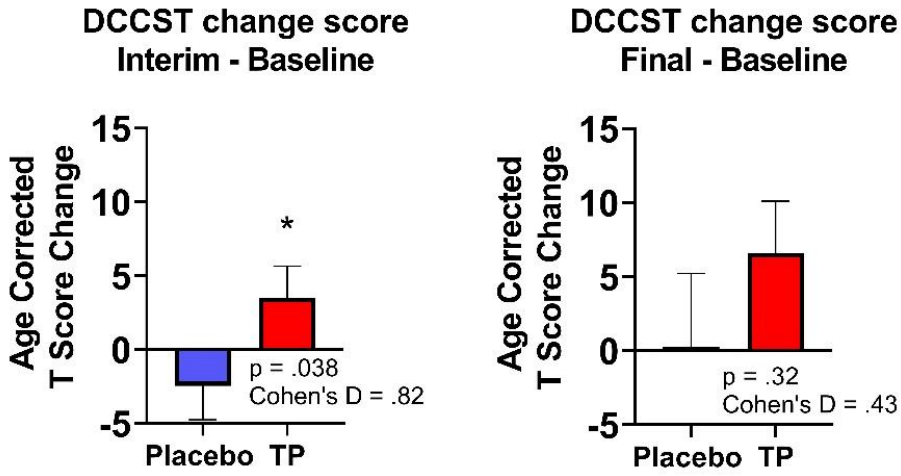

Figure 1. Changes from baseline in age-corrected t score of Dimensional Change Card Sort Task at the interim (Week 3) and final (Week 6) study visits. Bar graphs represent means ± SEM. DCCST, Dimensional Change Card Sort Task; TP, test product (MBB)

To analyze daily diary scores for changes in self-reported mind-wandering, a 2 X 3 (Group x Time) repeated measures ANOVA was carried out. There was no significant main effect of group or time or a significant effect of group x time interaction. None of the between-group comparisons of the weekly average of diary scores were significant.

To analyze systolic and diastolic blood pressure and heart rate, a 2 X 3 (Group x Time) repeated measures ANOVA was carried out. There was no significant main effect of group or time, or a significant effect of group x time interaction.

An independent samples t tests did not show a significant difference in compliance rates between the test product group (mean = 92%, SD = 0.06) and the placebo group (mean = 91%, SD = 0.05) [t(20) = 0.37, p = 0.83].

Discussion

This was a randomized, placebo-controlled, double-blind study to assess the effects of MBB on cognition in healthy teenagers. Teenagers can experience nutrition insufficiencies as well as dietary gaps. Therefore, nutritional interventions that support cognition during school years can be beneficial to this group. This is especially true given that there is an increased prevalence of obesity co-occurring with micronutrient deficiencies in teenagers — especially in low to middle income areas [22]. In summary, there were no significant differences between the groups in the change from baseline to the interim visit (Week 3) or from baseline to the final visit (Week 6) on measures of executive cognitive function, attention and executive cognitive function, cognitive processing speed or working memory, except in one case. Compared to the placebo group, the MBB group demonstrated a significantly better change from baseline at the interim visit in measures of executive cognitive function, as assessed by the Dimensional Change Card Sort Task. While this same pattern was apparent on the final visit, it was no longer statistically significant. There was no significant difference in heart rate or blood pressure between the groups.

It is uncertain why the MBB condition appeared to only influence performance on the Dimensional Change Card Sort Task. Unlike the other study tasks, this task assesses executive function in adolescents by sorting test cards by either color or shape. In particular, the executive processing involved in this task reflects shifting performance but not inhibition or speed of processing [23]. Given that the sample size for this study was relatively small, it is reassuring that the effect sizes for the DCCST are large for the interim change score and medium for the final visit change score since

he effect size provides a reasonable estimate of the size of the effect in replication (as opposed to the statistical significance level which depends on sample size in replication).

Previous research has shown that individual components of MBB influence executive function. For example, PS derived from soybeans significantly improved executive function in a population of older adults with memory-related complaints [24]. Pyrroloquinoline improved executive function in a group of healthy adults aged 40-80 [25]. Another study involving high-risk tactical operators following 24 hours of sleep deprivation found that all participants in the group supplemented with spearmint extract containing rosmarinic acid showed improved executive function, while that was observed in only 60% of participants in the placebo group [26]. Alpha-GPC has not been shown to specifically benefit executive function; however, as a biosynthetic precursor of acetylcholine, it shows promise in the treatment of cognitive decline and cognitive recovery [27]. This is the first study, to our knowledge, to show that the combination of these ingredients may improve a measure of cognition in healthy teenagers. It is possible the lack of an effect of MBB on all measures of cognitive functioning in this group is due to the developmental trajectory of these cognitive functions during adolescence [28].

One potential limitation in the present study was the relatively small sample size (n= 24). However, even with this limited sample, the major finding was sufficiently robust to yield statistical significance in the between-group difference in the Dimensional Change Card Sort Task at the conventional level with a large effect size. Nevertheless, the results should be interpreted with caution given that this is the first study to assess MBB in healthy teenagers. These results will need to be replicated in future work.

Conclusions

This study suggests that MBB potentially improves executive processes, but not other cognitive measures in healthy teenagers; this effect was only significant at the interim visit. Therefore, it is uncertain if there are any lasting beneficial effects. Further research should be conducted in a larger group of participants and focus on broader measures of executive function.

Conflict of Interest

This study was funded by Hong Kong Prospect Group Co. Limited. This funding source had no role in study design, data collection, analyses, interpretation of the data, decision to submit the manuscript, or writing of the manuscript.

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