

Brahmi for the better? New findings challenging cognition and anti-anxiety effects of Brahmi (*Bacopa monniera*) in healthy adults

Vidya Sathyanarayanan · Tinku Thomas ·
Suzanne J. L. Einöther · Rajendra Dobriyal ·
M. K. Joshi · Srinivasan Krishnamachari

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Abstract

Rationale A number of studies have indicated positive effects of long-term administration (3 months) of *Bacopa monniera* (Brahmi) on various cognitive functions especially memory and anxiety. However, inconsistent results in literature may be linked to various methodological issues.

Objective The present study aimed to test the chronic effects (12 weeks) of 450 mg of a *B. monniera* (Brahmi) extract on learning and memory, information processing and anxiety in healthy adult Indian population.

Methods The study design was a randomised, double-blind, placebo-controlled parallel design. Participants comprised of 72 healthy urban adults, both men and women, in the age range of 35–60 years who were educated and English speaking with basic knowledge of computers from Bangalore. The outcome measures included verbal learning and memory, inspection time, attention and interference. State and trait anxiety were additional outcome variables.

Results In the present study, there were no significant differences between the two groups on any of the cognitive

measures. However, there was a trend for lower state anxiety in the *B. monniera* (Brahmi) group as compared to placebo group.

Conclusions The current study attempted to determine the chronic effects of single daily dose of 450 mg of *Brahmi* extract on cognitive performance and anxiety in healthy adults. The results of the current study are not in agreement with findings of some of the earlier studies which have found improvement both on cognitive parameters and a reduction of anxiety scores.

Keywords *Bacopa monniera* · Brahmi · Cognitive functions · Memory · Anxiety

Introduction

Brahmi is the Sanskrit name for the herb *Bacopa monniera* L., of the Scrophulariaceae family, and has traditionally been used in Ayurvedic medicine for the promotion of memory, intelligence and the treatment of anxiety and stress-related conditions. Chemically, the therapeutic actions of Brahmi are attributed to a group of saponins present in the plant (Chatterjee et al. 1963; Basu et al. 1967). While initial studies revealed that primarily bacosides A and B are responsible for the effect of Brahmi, Kawai and Shibata (1978) showed that bacosides A and B themselves are mixtures of saponins.

Several animal studies investigated the memory-enhancing and anti-stress properties of Brahmi. In a series of studies, Singh and Dhawan (1982, 1997) reported better acquisition, improved retention and delayed extinction on shock-motivated brightness discrimination, active conditioned flight reaction and continuous avoidance tasks

V. Sathyanarayanan (✉) · S. Krishnamachari
St. John's Medical College Hospital, Bangalore, India
e-mail: vidyasnarayanan@gmail.com

T. Thomas · S. Krishnamachari
St. John's Research Institute, Bangalore, India

S. J. L. Einöther
Unilever R&D, Olivier van Noortlaan 120,
3133 AC Vlaardingen, The Netherlands

R. Dobriyal · M. K. Joshi
Unilever R&D, 64 Main Road, Whitefield,
Bangalore 560066, India

following Brahmi administration. Others have confirmed these memory enhancement effects (Singh et al. 1988; Vohora et al. 2000; Das et al. 2002; Kishore and Singh 2005; Joshi and Parle 2006) and reported Brahmi's anti-stress (Kar Chowdhuri et al. 2002; Sairam et al. 2002) and behavioural effects (Deepak and Amit 2004; Singh and Dhawan 1982; Singh et al. 1988; Singh and Dhawan 1997).

Effects of Brahmi on human cognitive function and stress have been investigated across different age ranges, from children to the elderly, and in both healthy and clinical populations. Initial studies conducted in India mainly involved clinical populations, patients with anxiety (Singh and Singh 1980) or mild to severe mental deficiency (Agrawal et al. 1990; Agrawal et al. 1993), students with poor educational performance (Dubey et al. 1994) or children (Sharma et al. 1987; Negi et al. 2000; Usha et al. 2008). Most studies consistently reported improved learning or memory, as well as some improvements in attention. However, methodological shortcomings, including lack of blinding or a placebo group, bias for practice effect, lack of validity of tools used and small sample sizes, preclude definitive conclusions.

More recently, several double-blind, placebo-controlled studies have investigated the effects of Brahmi on cognitive function. Although Brahmi did not have acute effects on performance (Nathan et al. 2001), chronic effects have been identified. In their first study with 46 subjects (aged 18–60 years), Stough et al. (2001) found that 300 mg Brahmi improved a number of outcomes on the Rey Auditory Verbal Learning Task (RAVLT), including learning rate, forgetting rate, proactive interference, as well as inspection time, and state anxiety as compared to the placebo. In a later study with 62 subjects (aged 18–60), Stough et al. (2008) reported Brahmi to significantly improve performance on the 'working memory' factor. Specifically, spatial working memory accuracy increased, and the number of false-positives on a Rapid Visual Information Processing (RVIP) task decreased. Others have examined the effect of Brahmi on age-related memory decline. In a study of 76 adults (aged 40–65), 300 mg Brahmi improved retention of new information, and on follow-up, there was a decrease in the rate of forgetting of newly acquired information (Roodenrys et al. 2002). Similar findings were obtained by others in an elderly population with Brahmi having a positive effect on (logical) memory and paired associate learning (250 mg/day; Raghav et al. 2006), digit span (backwards), RAVLT and paired associates learning delayed recall (450 mg/day; Barbhaiya et al. 2008), on the RAVLT and the Stroop task (300 mg/day; Calabrese et al. 2008) and verbal learning, memory acquisition and retention on the RAVLT (300 mg/day; Morgan and Stevens 2010). In a systematic review of randomised controlled trials evaluating the cognitive enhancing effects of *Bacopa monnieri*/Brahmi, Pase et al. (2012) found evidence to suggest that *Bacopa* improves memory free recall

with little current evidence for enhancement in other cognitive abilities.

Thus, a number of studies have indicated positive effects of long-term administration (typically 3 months) of Brahmi on various cognitive functions. Unfortunately, results are far from consistent. Studies assessing verbal learning and memory (RAVLT) have found improved delayed recall (Pase et al. 2012; Morgan and Stevens 2010; Calabrese et al. 2008; Roodenrys et al. 2002), and one found improved learning rate (Stough et al. 2001) while others did not (Calabrese et al. 2008; Roodenrys et al. 2002). On tests that measured information processing, while the inspection time test was sensitive to the effects of Brahmi (Stough et al. 2001), a divided attention test did not find an effect of Brahmi on a similar threshold (Calabrese et al. 2008). Pase et al. (2012) suggest that research into the nootropic effects of *Bacopa* is in its infancy, with the effects of *Bacopa* across all human cognitive abilities yet to be investigated.

Likewise, inconsistent results were found for measures of anxiety (Calabrese et al. 2008; Roodenrys et al. 2002; Stough et al. 2001). The observed inconsistencies may be linked to various methodological issues. Most studies involved small sample sizes with a wide age distribution. In addition, gender has not received adequate representation in the samples. Also, assessment of multiple cognitive domains may have resulted in type I errors.

In view of the above lacunae in research in this area, this study proposed to examine the efficacy of the chronic effects of a standardized extract of Brahmi (*B. monniera* dried herb) on cognitive function and anxiety in a healthy adult Indian population using a double-blind, placebo-controlled design. Keeping in view the intrinsic multi-component nature of herbals and geo-climatic variations in the cultivars, it was imperative that the product be standardized to the extent that the variations of its components are kept within an acceptable range. In the present study, a specialized extract of Brahmi that was standardized for its chemical constituents was used. It was tested quantitatively for the presence of bacoside A3 (4.0–6.0 %), bacoside I (5.0–8.5 %), bacoside II (4.5–8.0 %), jujubogenin isomer of *Bacopa*, saponin C (5.0–8.5 %), bacopasaponin C (3.5–5.5 %), bacosine (1.0–2.0 %), luteolin (0.2–0.8 %), apigenin (0.1–0.4 %) and sitosterol-D-glucoside (>0.3 %).

Methods

Subjects

Previous studies indicate that including 30 subjects is suitable to estimate differences with sufficient precision (Stough et al. 2001; Calabrese et al. 2008). The sample size of 72 was arrived by doubling this number and adding 20 % to

manage possible dropouts. After taking the written informed consent, 164 volunteers were screened. Seventy-two healthy adults (21 males) in the age range of 35–60 years were enrolled in the study. Participants were English speaking with basic knowledge of computers from Bangalore, India, with BMI in the range of 20–30. The study was conducted between March and July 2010. The Institutional Ethical Review Board, St. John's Medical College, Bangalore approved the study.

Screening tools were the General Health Questionnaire (GHQ-28 Goldberg and Hillier 1979), Whisper Voice Hearing Test, Ishihara test for Colour Blindness and the Alcohol Use Disorders Identification Test (AUDIT-C; Babor et al. 2001), to control for the effects of alcohol on cognitive functions. Volunteers who scored above 9 on the GHQ-28 (Morris and Goldberg 1989) and reported high levels of depression or anxiety were excluded and offered a referral to mental health specialists in St. John's Hospital for further evaluation and treatment. In addition, the volunteers completed practice versions of the computerised tests (inspection time task and rapid visual information processing task), in order to assess their ability to perform these tasks.

Baseline assessment was carried out on 69 subjects and post-assessment was carried out with 66 subjects, as there were 3 dropouts during the study period. Thus, 33 subjects in each group completed the study. One adverse event of back pain was reported from the placebo arm of the study (Fig. 1).

Design

The current study employed a randomised, double-blind, placebo-controlled design with parallel groups. Volunteers were randomised into two treatment groups, Brahmi and placebo, balanced for age and gender. Volunteers were enrolled in a phased manner in groups of six subjects every day, over a 3-week period. Randomisation was performed by means of a computer-generated list using Ralloc software in blocks of six and the enrolled subjects were assigned intervention codes in sequence. The stratum were assigned to the eight different randomisation lists using random number tables. Randomisation codes took into account age, gender and education at two levels and were generated statistically. The researchers and participants were kept blind to treatment allocations. Randomisation was completed by a staff member at the institute who was not involved in the study. *Bacopa* and placebo treatments were given to subjects in identical bottles differentiated by a code. Statistical analyses were performed after deblinding the treatment allocation.

Intervention

Volunteers were instructed to consume two capsules amounting to 450 mg of either the placebo or Brahmi daily

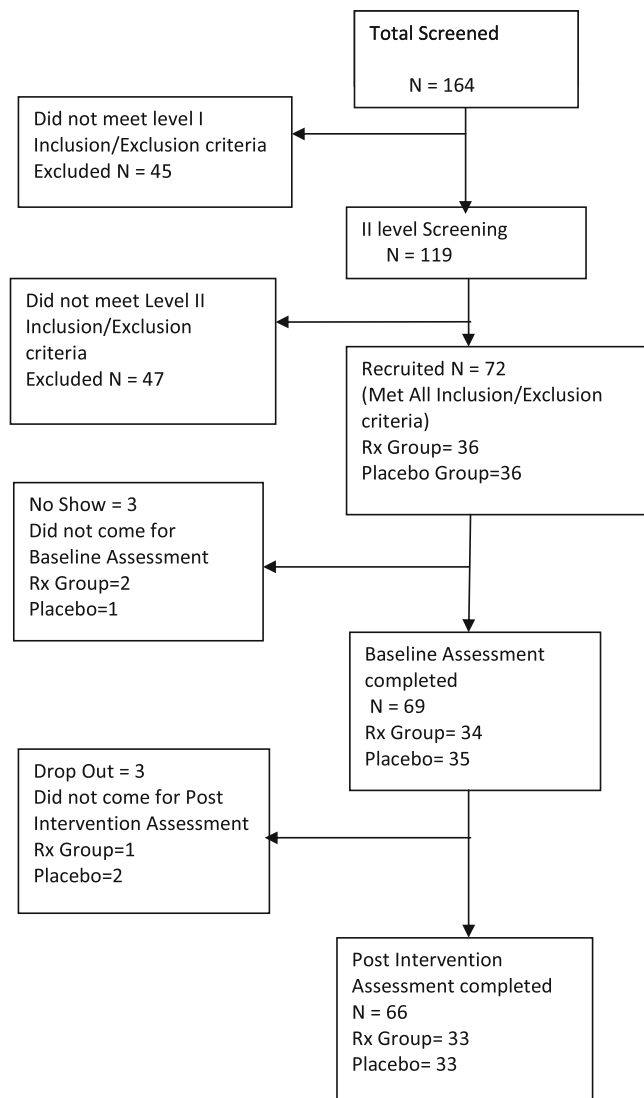


Fig. 1 Flowchart of subjects through screening, recruitment and intervention

after breakfast during the 12-week intervention period. One Brahmi capsule contained 225 mg of commercially available BacominTM along with approved excipient in '1' size hard gelatin capsule shell. Placebo capsules contained equal quantity of starch along with the same excipient in same size of hard gelatin capsule shell.

During the course of the study, participants were requested not to change their dietary habits. Furthermore, they were required not to take any additional products of Brahmi or any other nootropic agent during the study. Compliance was checked weekly through a diary provided for the purpose. Participants were prohibited from consuming alcoholic beverages and caffeine-containing products from 9 p.m. the day before the assessment. Compliance was checked with a saliva swab test for the presence of caffeine before the start of the cognitive assessments. Considering the 84-day duration of the

study, ± 3 days for the intervention period was determined as acceptable.

Cognitive performance

On each of the two measurement days (baseline and end point), the same test battery of 1 1/2 h was administered to the subjects by the same examiner. Tests of verbal learning and memory, inspection time, attention and interference and anxiety which showed significant effects of Brahmi in previous studies were included (Barbhaiya et al. 2008; Calabrese et al. 2008; Roodenrys et al. 2002; Stough et al. 2001, 2008). The test battery was administered in English. Subjects were examined in the morning at approximately the same time during both measurement days to keep conditions constant. The tests were administered in the order given below.

1. **Rey Auditory Verbal Learning Task:** The RAVLT (Rey 1964) is a measure of verbal learning and memory that is a validated and widely used test for assessing memory in both clinical practice and research (Lezak et al. 2004). It has been validated in the Indian setting and used as part of a neuropsychological test battery (Rao et al. 2004). The RAVLT assesses various aspects of memory and learning. Two parallel versions of wordlists A and B, matched for word frequency, word length and concreteness, were prepared for pre- and post-intervention testing to avoid learning effects. Outcomes were delayed recall, learning rate, total learning, proactive interference, retroactive interference and forgetting. Previously, 300 and 450 mg Brahmi daily for 12 weeks were found to improve performance on the RAVLT (Stough et al. 2001; Barbhaiya et al. 2008; Calabrese et al. 2008; Morgan and Stevens 2010).
2. **Inspection Time Task:** The Inspection Time (IT) task (Taylor and Creelman 1967; Bonney et al. 2006) measures information processing using a simple two-choice discrimination task. The stimulus consists of two parallel vertical lines, joined at the top by a horizontal bar. The two lines differ in length and the longer line can be either left or the right one. Participants were required to indicate which of the two lines is longer. Almost immediately after the stimulus is presented, a mask covers it to remove any iconic cues of the stimulus. The time between the stimulus and the appearance of the mask is varied to determine a person's information processing capability. IT is defined as the minimum exposure time to a stimulus that is required to reach a predetermined accuracy level of 80 %. Previously, Stough et al. (2001) found that 300 mg Brahmi daily for 12 weeks improved inspection time.
3. **Rapid Visual Information Processing Test:** The RVIP test (Wesnes and Warburton 1983) is another measure of information processing that contains a working memory component, as the participant was required to keep the numbers presented in their working memory. In this task, a series of single digit numbers (one to nine) is presented on the screen, one at a time, in quick succession for 7 min. The participant is required to respond whenever a row of three even numbers is presented (i.e. any three of 2, 4, 6, 8), without an odd number in between, or a row of three odd numbers in a row is presented (i.e. any three of 1, 3, 5, 7, 9) without an even number in between. The outcome measures are hit rate (the percentage of targets correctly detected), speed (the average reaction time in millisecond) and false alarm rate (the percentage of false-positives). Previously, Stough et al. (2008) found that Brahmi significantly decreased the number of false-positives on the RVIP.
4. **Stroop Task:** The Stroop task (Stroop 1935) measures attention and interference. In this study, the original card version was used. The outcome was the interference score (card 3). Previously, 300 mg Brahmi daily for 12 week was found to reduce interference on the Stroop task (Calabrese et al. 2008).
5. **State–Trait Anxiety Inventory:** The State–Trait Anxiety Inventory (STAI) (Spielberger 1979) is a measure of anxiety, which is used extensively in research and clinical practice. It comprises self-report scales for measuring state and trait anxiety and is scored on a four-point Likert scale. The test battery started with the STAI Y1 (State Anxiety) to prevent the performance on cognitive tasks from impacting anxiety outcomes. The STAI Y2 (Trait Anxiety) was administered at the end of the session to reduce context effects.

Statistical analyses

The primary analysis was an ANCOVA for significance of effects of the intervention on the primary outcome measure RAVLT delayed recall with intervention group as the factor, after including the baseline score as a covariate. Similarly, ANCOVA was performed on each of the secondary endpoints. Missing, unused and inconsistent data were not replaced. All analyses were carried out after excluding the missing data.

Endpoint measures when found to be significantly deviating from normality on examination by skewness and QQ plots, appropriate transformations were done for the parameter, and ANCOVA was performed on the transformed values. Only data on subjects with both the baseline and endpoint assessments were considered for the analysis and any missing values were not replaced. Data of three subjects each who dropped out were missing in both study arms. In addition, three subjects who were outliers on specific cognitive tests (IT and RVIP) were excluded from analyses. Alpha was set at 0.05. All analysis was performed using SAS 9.1 statistical software.

Results

Socio-demographic characteristics of the sample are detailed in Table 1. The mean age of the sample was 42 years (± 6.9). There was no significant difference in age between the treatment and placebo conditions. Subjects recruited were predominantly female (68.2 %) and the two groups did not differ significantly in their gender composition. Most subjects were graduates and the two groups did not differ with regard to education. The mean BMI of the group was 26.0 (SD=2.4) with no significant difference between the treatment and placebo groups. The compliance rate for the whole group was 97.1 %, with compliance in the treatment arm being 97 % and compliance in the control arm being 98 %.

Table 2 summarises the findings on all the cognitive and anxiety parameters. On the RAVLT delayed recall, the primary efficacy parameter, there were no significant differences between the treatment and placebo group. In addition, there were no significant differences between the groups on the various secondary efficacy parameters on the RAVLT (learning rate, total learning, proactive interference and retroactive interference), IT, RVIP and the Stroop test. There were no significant differences between the two groups on the state (STAI Y1) and trait measure of anxiety (STAI Y2).

Discussion

The current study attempted to determine the chronic effects of single daily dose of 450 mg of *Brahmi* extract on cognitive performance and anxiety in a carefully selected group of healthy Indian adults. Using a randomised, double-blind, controlled design, no significant differences were found between the two groups on any of the cognitive or anxiety measures.

The results of the current study are not in agreement with findings from earlier studies on *Brahmi*, as previous studies found improvement both on cognitive parameters and a

reduction of anxiety scores. The differences in results regarding cognitive performance between the current and previous studies could be related to differences in the study population. In the current study, a normal Indian adult population aged 35 to 60 years was selected, for theoretical as well as practical reasons. In contrast, studies that have reported positive effects of *Brahmi* on cognitive measures involved elderly subjects (Morgan and Stevens 2010; Calabrese et al. 2008) suggesting that *Brahmi* might have a greater impact in an older population. Similar observations have been made from animal models, wherein *Brahmi* attenuated experimentally induced amnesia and decrements in memory linked to aging (Vohora et al. 2000; Joshi and Parle 2006; Prabhakar et al. 2008; Holcomb et al. 2006).

In addition, the possibility of dose effect of *Brahmi* needs consideration as this study evaluated the effect of 450 mg of *Brahmi*, whereas other studies have reported positive effects with a dosage of 300 mg/day for 12 weeks (Morgan and Stevens 2010; Calabrese et al. 2008; Stough et al. 2001).

Our findings further stress the inconsistency of *Brahmi* effects in healthy adults. Specifically, of the studies that assessed verbal learning and memory using the RAVLT, some have found an effect of *Brahmi* on delayed recall (Pase et al. 2012; Morgan and Stevens 2010; Calabrese et al. 2008; Roodenrys et al. 2002) and one found improved learning rate (Stough et al. 2001) while others did not (Calabrese et al. 2008; Roodenrys et al. 2002). In addition, while a measure of inspection time was sensitive to the effects of *Brahmi* in the study by Stough et al. (2001), this was not substantiated in the current study.

The nature of product (*Brahmi*) used in intervention is also variable across studies with most studies using ethanol extracts ranging from 3 g of the dried herb per capsule (Roodenrys et al. 2002; Raghav et al. 2006; Barbhैया et al. 2008; Usha et al. 2008) to 15 g of the herb and 150 mg of bacosides A and B (Calabrese et al. 2008). This variability in composition of *Brahmi* makes it difficult to permit conclusions and attribute effects to specific components.

Table 1 Baseline subject characteristics

Variable	Statistic	Total (N=66)	Treatment (N=33)	Placebo (N=33)	p value
Age in years	Mean (SD)	42.1 (6.9)	42.9 (7.5)	41.3(6.3)	0.34
Male	N (%)	21 (31.8)	10 (30.3)	11 (33.3)	0.79
Female	N (%)	45 (68.2)	23 (69.7)	22 (66.7)	
Level of education					
Higher secondary	N (%)	16 (24.2 %)	8 (24.2 %)	8 (24.2 %)	0.54
Diploma	N (%)	2 (3 %)	0 (0 %)	2 (6.1 %)	
Graduate	N (%)	38 (57.6 %)	19 (57.6 %)	19 (57.6 %)	
Post-graduate	N (%)	10 (15.2 %)	6 (18.2 %)	4 (12.1 %)	
Weight in kg	Mean (SD)	65.9 (8.5)	66.0 (7.4)	65.8 (9.6)	0.92
Height in m	Mean (SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.47
BMI group	Mean (SD)	26.0 (2.4)	26.3 (1.9)	25.8 (2.8)	0.36
% Compliance	Mean (SD)	97.1 (4.1)	96.6 (4.8)	97.6 (3.3)	0.32

Table 2 Chronic effects of Brahmi (450 mg) on RAVLT, IT, RVIP, Stroop and STAI Y1 and STAI Y2 between the two intervention groups (mean±SD)

Test	Baseline		Endpoint		F value	p value
	Brahmi N=33	Placebo N=33	Brahmi N=33	Placebo N=33		
RAVLT delayed recall	11.55±2.72	12.18±2.23	11.97±2.56	12.91±1.77	1.73	0.1930
RAVLT learning	4.85±1.94	5.88±2.04	5.27±2.45	5.73±2.18	0.13	0.7202
RAVLT total learning	55.67±7.30	56.00±8.02	55.79±7.11	58.09±7.05	2.62	0.1105
RAVLT proactive interference	-2.06±2.19	-0.12±2.83	-0.88±1.76	-1.18±2.28	0.89	0.3480
RAVLT retroactive interference	1.18±1.93	1.00±2.28	0.79±1.82	1.15±1.64	1.26 ^c	0.2660
RAVLT forgetting	0.12±1.71	-0.03±1.74	-0.21±1.41	-0.33±1.57	0.10	0.7585
Inspection time	98.64±31.29 ^b	98.30±31.26 ^b	100.34±42.43 ^b	99.33±30.61 ^b	0.08 ^a	0.7764
RVIP hit rate	31.10±11.26 ^b	32.30±11.11	31.47±13.62 ^b	33.30±10.82	0.43 ^c	0.5165
RVIP false alarm rate	9.94±12.99	13.94±13.43	13.47±14.47	14.39±19.01	1.31 ^a	0.2561
RVIP sensitivity	0.59±0.24	0.66±0.26	0.64±0.27	0.68±0.30	0.38 ^c	0.5392
RVIP reaction time	520.46±76.13 ^b	522.49±64.76	519.86±65.15	509.61±65.89	0.96	0.330
Stroop	-0.55±5.48	-1.08±8.13	-0.28±5.96 ^b	-0.01±8.36 ^b	0.33	0.5661
STAI Y1	25.66±6.67	27.79±7.92	24.25±5.22 ^b	27.33±6.44	3.13 ^a	0.0819
STAI Y2	33.85±8.12	34.70±7.84	31.30±8.97	33.52±8.80	1.09	0.2994

ANCOVA was performed to compare the mean scores of the intervention groups at endpoint

^a ANCOVA performed on natural log-transformed scores of the intervention groups at endpoint

^b N ranges between 31 and 32

^c ANCOVA was performed on square root-transformed scores of the intervention groups at endpoint

In the present study, Brahmi did not have any statistically significant effect on trait anxiety as measured on STAI. With regard to state anxiety, although the group as a whole reported low scores at baseline, subjects that received Brahmi compared to placebo reported less state anxiety at endpoint, although this trend was not statistically significant. Many others have emphasized the anxiety-reducing effects of Brahmi (Singh and Singh 1980; Calabrese et al. 2008). However, comparing the anxiety-reducing effects of Brahmi across studies is difficult, as different measures of anxiety have been used by different investigators. In the present study, the use of stringent criteria for selection of volunteers resulting in the exclusion of subjects with anxiety by using the GHQ may have masked the anti-anxiety effects of Brahmi. It is possible that the anti-anxiety effects of Brahmi are more likely to be apparent in trait anxious subjects rather than in a healthy normal population with minimal or no experience of anxiety.

The strengths of the current study include a robust design, the use of stringent inclusion and exclusion criteria, adequate sample size and controlling for various confounders, including dietary restrictions such as caffeine that could have influenced cognition. Participants were screened for the use of Brahmi, cognition-enhancing supplements and psychoactive substance use although concurrent use of other medications that could have impacted cognition (such as

statins) was not specifically checked. The use of validated computer-based tests for some of the cognitive measures is yet another positive feature of the study. Earlier studies have shown that computer-administered cognitive tests result in less variability in test administration (Wesnes et al. 1999a; b). In addition, the use of parallel forms of the RAVLT, which is the primary outcome measure to test the impact of intervention, attenuates practice effects of repeat administration of cognitive tests (Wesnes 2010). The compliance rate in the consumption of the product was very good. Finally, the Brahmi products were standardized to the extent that the variations of its components were kept within an acceptable range. A limitation of the current study could be the characteristics of the study population. The cognitive and anti-anxiety effects of Brahmi could be less apparent in a sample of healthy subjects with minimal anxiety as there may be little scope for improvement with Brahmi supplementation in a sample of high functioning individuals. In addition, the cognition-enhancing effects of Brahmi may be more apparent in an older age group as compared to this sample. Screening for cognitive status or intellectual functioning of the subjects studied would have increased the robustness of the study.

In conclusion, although previous studies and Indian traditional medicine have suggested beneficial effects of Brahmi, these effects could not be replicated in the current well-designed study. Administration of Brahmi across

12 weeks had no significant effect on cognitive functions and state and trait anxiety in normal adult human subjects.

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Conflict of interest S. Einöther, R. Dobriyal, and M. Joshi are employees of Unilever. One of the Unilever-operating companies, Hindustan Unilever Ltd., has two products that contain Brahmi in the market. V. Sathyanarayanan, T. Thomas and K. Srinivasan have no conflict of interest to report.

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