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Posibles beneficios mentales y físicos de la suplementación con un preparado multivitamínico/mineral del complejo B en dosis altas: ¿Qué evidencia hay?

Potential mental and physical benefits of supplementation with a high-dose, B-complex multivitamin/mineral supplement: What is the evidence?

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Posibles beneficios mentales y físicos de la suplementación con un preparado multivitamínico/mineral del complejo B en dosis altas: ¿Qué evidencia hay?

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ABSTRACT

Objective: to perform a systematic literature review to examine the effects of high-dose, B-complex multivitamin/mineral supplementation on physical, mental, and energy outcomes in healthy and 'at-risk' (suboptimal nutritional status/subclinical symptoms at baseline) adult populations.
Methods: PubMed was searched for relevant randomized controlled trials until January 2020.
Results: overall, 136 publications were identified. In the seven randomised, double-blind, placebo-controlled studies considered eligible for inclusion, supplementation in healthy populations predominantly showed improvements in perceived stress, physical stamina, concentration, and general mental health, and significant reductions in anxiety and improvements in self-reported vigour. However, not all of these outcomes were significant, and statistical correction for multiple outcomes was not commonly employed. Studies investigating brain mapping following supplementation indicated increased functional activity in brain regions related to processing of attention, executive control, and working memory during cognitive tasks.

Conclusions: while there is certainly a need for further studies on the neurocognitive and physical benefits of micronutrient supplementation, this review provides generally supportive evidence for the benefits of a high-dose, B-complex multivitamin/mineral supplement in healthy and at-risk populations in terms of physical, mental, and energy outcomes.

Keywords: B vitamins. Energy. Mental outcomes.

RESUMEN

Objetivo: realizar una revisión sistemática de la literatura para valorar los efectos de la administración de suplementos multivitamínicos/minerales del complejo B en dosis altas sobre los resultados físicos, mentales y energéticos en poblaciones adultas sanas y en situaciones especiales de riesgo (estado nutricional subóptimo/síntomas subclínicos al inicio del estudio).

Métodos: se realizaron búsquedas en PubMed de ensayos controlados aleatorios relevantes hasta enero 2020.

Resultados: en total se identificaron 136 publicaciones. En los siete estudios aleatorizados, doble ciego y controlados con placebo considerados elegibles para la inclusión, la suplementación en poblaciones sanas mostró predominantemente mejoras en la percepción del estrés, la resistencia física, la concentración y la salud mental general, así como una reducción significativa de la ansiedad y mejoras en la vitalidad según la autoevaluación de los participantes. Sin embargo, no todos estos resultados fueron significativos y la corrección estadística para múltiples resultados no se empleó habitualmente. Los estudios sobre el mapeo cerebral después de la suplementación, indicaron un aumento de la actividad funcional en las regiones del cerebro relacionadas con el procesamiento de la atención, el control ejecutivo y la memoria de trabajo durante tareas cognitivas.

Conclusiones: si bien ciertamente existe la necesidad de realizar más estudios sobre los beneficios neurocognitivos y físicos de la suplementación con micronutrientes, esta revisión proporciona evidencia en general sobre los beneficios de un suplemento multivitamínico/mineral del complejo B en dosis altas, en poblaciones sanas y en situaciones de riesgo, en términos de resultados físicos, mentales y energéticos.

Palabras clave: Vitaminas B. Energía. Resultados mentales.

INTRODUCTION

The consequences of micronutrient deficiencies in the general population are widespread. With respect to the potential association between micronutrient status and neurological health, epidemiological studies have revealed a correlation between low biochemical levels of micronutrients and poor cognitive function and mood, leading to a range of symptoms (1,2). Optimal nutrition is known to positively contribute to both mental and physical performance, with data indicating that the impact of certain micronutrients, specifically B and C vitamins, calcium, magnesium and zinc, may be of particular importance in supporting cognitive function (2-4). Deficiencies in folate, vitamin B12 and other B vitamins are also known to contribute to physical fatigue (2-5).

Vitamins and minerals are not synthesised endogenous to the human body and therefore must be consumed as part of a balanced diet. In support of this, the governments of most developed nations provide recommended dietary intakes of vitamins and minerals. Such recommendations are intended to guide populations on the advised intake of individual micronutrients that should prevent micronutrient deficiency in the vast majority of the population (1,4). However, despite the availability of this guidance (which generally only reflects

the bare-minimum levels to mitigate deficiency-based diseases, and not for optimal health), low intake of micronutrients is prevalent even in apparently healthy populations in developed countries (3,4). Evidence suggests that this is particularly the case in the young and elderly, and in middle-aged adults exposed to high occupational pressures. These include students, working professionals, multi-tasking parents, and those with an active lifestyle (3,4). Reasons for not achieving sufficient micronutrient intake may include lifestyle-associated behaviours, such as rushed meals (related to poor digestion), unhealthy food choices, chronic or periodical dieting, and stress-related activities, such as smoking and excessive consumption of coffee or alcohol (3,4). The prevalence values for B vitamin deficiency differs across age groups, sex, socioeconomic groups, and developed geographies, with evidence suggesting that insufficiency can vary vastly, with values of less than 5 % reported in the UK population and 10.5 % reported in the United States, compared with up to 54 % in the Netherlands (4,6,7).

Micronutrients play an important role in normal physiology and healthy bodily functions, with B vitamins performing coenzyme functions essential to the biochemistry that underpins energy, fat and protein metabolism, cell growth and function, and nucleic acid synthesis and repair (1,3,4). In addition, adequate levels of micronutrients are required to maintain optimal functioning of the central nervous system (CNS) and facilitate cognitive processes, with insufficient levels of micronutrients known to impair cognitive and physical function (2-4). Inadequate levels of micronutrients can also result in reduced neurotransmitter levels, diminished structural and functional integrity of neuronal membranes and receptors, and impaired energy production that can affect cognition (1-4,8). Deficiency of vitamins B6, B9 and B12 have also been linked to the potentially neurotoxic accumulation of homocysteine, which may impair cognitive function and mood, and has been observed in a range of pathologies (4). The essential cofactor role of B vitamins in

the one-carbon cycle, specifically, has contributed to the hypothesis linking B vitamin levels with mood (9). Mitochondrial functions are also compromised by insufficient dietary intake of B vitamins and/or increased B vitamin needs (4). While there is limited clinical data on the interactions between micronutrient metabolism and physical performance, it has been shown that deficiencies in certain B vitamins can contribute to physical fatigue (2-4).

The clinical importance of even mild micronutrient deficiencies should not be underestimated, due to the risk of predisposing individuals to increased risk of poor health. Specifically, while overt micronutrient deficiency is known to contribute to changes in behaviour, a marginal B vitamin deficiency can potentially lead to symptomatic changes in psychological parameters (3,4). Such symptoms of marginal micronutrient deficiency include fatigue, weakness, loss of concentration, depressed mood, neurological disturbances, and anxiety (3,4). Therefore, one might not be surprised to learn that deficiencies of micronutrients may have wide reaching consequences on a population level, translating to loss of productivity in the workplace and increased healthcare costs, with subsequent economic implications (10-12).

Therefore, it stands to reason that micronutrient supplementation may in part assist in attenuating a negative health status in the general population. In support of this, evidence suggests that supplementation with multivitamins/minerals may enhance cognitive and physical function in both healthy and ‘at-risk’ populations, including those with suboptimal nutritional status for any reason (1,3,4,9). While the effect of intervention with a single or restricted range of micronutrients is limited, nutritional supplementation has already been shown to enhance cognitive and psychological functioning (2,4). In fact, the benefit of supplementation with multiple B group vitamins on stress in healthy and at-risk populations has been observed in a recent systematic review and meta-analysis (9).

To our knowledge, there are a vast array of products sold worldwide that provide differing formulations of vitamins and minerals; however, we believe there is generally little research conducted to determine the clinically meaningful benefits that these provide to healthy populations. Thus, our systematic review aimed to investigate the effects of supplementation with a high-dose B-complex multivitamin/mineral supplement on mental and physical health, by assessing physical, mental and energy performance outcomes. The supplement (Berocca® Performance, Bayer Consumer Health) is designed to support mental and physical performance and energy. Its specific formulation was amended in 1998 to include vitamins B1 (15 mg), B2 (15 mg), B6 (10 mg), B12 (10 mcg), C (500 mg), biotin (150 mcg), folic acid (400 mcg), nicotinamide (50 mg), and pantothenic acid (23 mg), and minerals calcium (100 mg), magnesium (100 mg), and zinc (10 mg). A review paper authored by Maggini and colleagues in 2014 evaluated the evidence available on the effect of both the previous and current formulations of Berocca on cognitive function (2). Our review aimed to update and extend these findings by evaluating more recent evidence from randomised controlled trials (RCTs) on the effects of supplementation with the newest, currently available formulation of Berocca on mental but also on physical parameters, and the close interdependence of the two in healthy subjects.

METHODS

The primary focus of this review was to evaluate the effects of the high-dose B-complex multivitamin/mineral supplement on health status, including mental and physical domains. PubMed was searched for randomized controlled trials until January 2020 by using the following search string: (multivitamins[Title] OR multivitamin[Title] OR b vitamin complex[Title] OR multi-vitamin[Title] OR Multi-Vitamin/Mineral[Title] OR multi vitamin[Title]) (mental OR

psychological OR cognition OR cognitive OR neurocognition OR neurocognitive OR energy OR stamina OR performance OR fatigue). Search results were manually filtered to remove all non-human and *in vitro* studies. For the selection process, see figure 1.

The initial search captured 136 records. After screening of titles and articles, 68 *in vitro* and non-human studies were excluded. Following this, 68 full-text articles were manually filtered to remove articles focussed on unspecified multivitamins or which did not consider a physical, mental or energy performance outcome. Seven articles fulfilled the inclusion criteria and were included in this review (Table I).

RESULTS

Efficacy of supplementation: evidence from RCTs

Table I provides an overview of the seven eligible studies identified from the systematic literature search. All relevant outcomes from these studies have been included to ensure the efficacy of supplementation with this high-dose B-complex multivitamin/mineral supplement can be sufficiently discussed. Each study discussed here employed up to date methodologies, and these have been detailed in the Appendix.

Cognitive performance

The supplement has been investigated in seven RCTs in healthy populations, with outcomes demonstrating enhanced mental performance that may be supported by parameters of brain activity, cognitive performance and concentration, as discussed below.

Supplementation for 28 days may improve the ability to concentrate, as demonstrated by 80 healthy men who reported an improvement in concentration via rating scales (13). In addition, healthy males receiving this high-dose B-complex multivitamin/mineral supplement

for 33 days presented with improved cognitive performance and reduction in mental tiredness during a 60-minute cognitive demand battery (CDB) of tasks designed to assess the impact of treatment on speed/accuracy and mental fatigue, and which has been shown to be sensitive to a number of different supplements (14). A concomitant study that involved these same male participants required them to complete intense cognitive tasks in a 'Mobile Phone Battery' study, a form of testing shown to be sensitive in assessing aspects of cognitive performance and delivering mood visual analogue scale (VAS). Following supplementation for 28 days, this concomitant cohort presented with results revealing significant improvements in concentration and significant, sustained increases in alertness and mental stamina (15).

Brain mapping studies have shown that the effects of supplementation on functional brain activity can be seen as soon as 30 minutes after one dose (16,17), although long-term supplementation of four weeks appears necessary for significant improvements in cognitive outcomes, such as mental fatigue, mental stamina, and concentration (13-15,18), which may translate into clinically important improvements.

Whole-brain analysis of participants during a working memory/vigilance task (rapid visual information processing; RVIP) and following supplementation indicated significantly increased functional brain activity in regions associated with working memory and attention, including the right precentral gyrus, and the left and right cerebellum (Fig. 2) (16). Furthermore, the high-dose B-complex formulation resulted in response patterns in the frontal cortex that are indicative of greater activation of task-relevant frontal brain regions, as measured by significant, transiently reduced amplitude and phase advance in the steady-state visually evoked potential (SSVEP) response during completion of the active continuous performance task (A-X CPT; Fig. 3) (17). The narrow-band characteristics of the

SSVEP permitted reduced susceptibility to noise contamination, and improved detection.

In a pilot 'brain mapping' study, participants undergoing neurocognitive assessment 30 minutes after intake of this high-dose B-complex multivitamin/mineral supplement experienced an increased efficiency of cortical functioning, as determined by steady-state topography (SST) (16). In a subset of participants, this formulation was also shown to increase activation in brain regions that constitute a well-established fronto-parietal working memory network (2,16). Furthermore, converging evidence from functional magnetic resonance imaging (fMRI) and SSVEP recordings in another brain mapping study demonstrated brain activity patterns consistent with centro-parietal regions following supplementation (18). To our knowledge, Berocca was the first multivitamin/mineral preparation to be studied for neurocognitive benefits using fMRI, which enables simultaneous capture of both behavioural data and brain activity, with high spatial resolution that surpasses that of functional near-infrared spectroscopy (16,18). We also understand that the use of fMRI to specifically examine the effects of multivitamin/mineral supplementation on brain activation was first employed by Scholey *et al.*, then in a further two studies (16-18). Overall, findings from these mapping studies support acute activation of the human brain regions linked to attention, executive control and working memory (16-19).

Perceived energy levels

In a large study of 215 healthy participants, 33 days of supplementation was associated with a significant increase in self-reported physical vigour, as assessed by the Profile of Mood States (POMS) questionnaire, a highly reliable, valid and well-established measure of psychological distress (14). Furthermore, a significant and sustained increase in physical stamina in the morning and evening was self-reported via VAS by 198 male participants receiving the

supplement for 28 days (15). Data from a study in 80 healthy males also indicated that it may protect against minor illness, as those receiving placebo for 28 days registered a significant increase in somatic symptoms that was not observed in those receiving the high-dose B-complex formulation for 28 days (13). Somatic symptoms assessed during the study included watery eyes, upset stomach, congested nose, headache, feverishness, aches, ringing in the ears, eye strain and sore throat, amongst others (13).

Stress, mood, and biochemical outcomes

Dietary supplementation with this high-dose, B-complex multivitamin/mineral supplement has been associated with significant improvements in mood, compared with baseline and placebo, as demonstrated by increased vigour-activity and decreased depression-dejection (14,19). Significant reductions in stress, subjective stress and anxiety and numerical reductions in stress-related symptoms have also been observed across psychometric instruments known to reliably assess psychological status, including the General Health Questionnaire (GHQ), POMS and Hospital Anxiety and Depression Scale (HADS) questionnaires (13,14). While a direct link between supplementation and enhanced performance was not measured in all of these studies, the findings suggest an improvement in wellbeing and ability to effectively cope with stress and anxiety in daily life (13,14,19).

White *et al.* conducted a blood biochemical assessment in which significantly greater levels of vitamins B6 and B12 and significantly reduced levels of homocysteine were observed following 28 days of supplementation compared with placebo (19). Non-significant increases in levels of red blood cell folate and plasma zinc have also been observed following 28 days of supplementation (18,19). Of interest, the findings from White *et al* corroborate those of a previous study, in which participants also experienced significant reductions in

homocysteine levels (20). These findings appear promising, given the evidence that a deficiency in certain B vitamins can lead to accumulation of homocysteine and decreased synthesis of monoamines, which may ultimately affect mood (5,21,22).

Finally, adverse events were either not reported or those reported were not serious and did not result in any treatment discontinuations.

Real-world studies may be considered an increasingly credible study type, as they are often able to examine large, heterogenous populations for long durations. There is certainly a need for such studies on the use of multivitamin/mineral supplementation in large patient populations and subpopulations/at-risk groups (with suboptimal nutritional status or subclinical symptoms at baseline) (1). Despite some obvious methodological limitations, such as their typically observational or retrospective nature, these studies would strengthen the current understanding of the influence of micronutrient status and dietary habits on the effects of supplementation. One such study followed 300 male and female university students preparing for upcoming examinations who were taking either Berocca or no vitamin/multivitamin supplement at all. Participants were asked to complete questionnaires for assessment of their memory, concentration and stamina. Two hundred also completed 10-15-minute cognitive assessments via a verbal reasoning task to assess verbal learning, a stroop task to assess focus, and a digital span task to assess working memory and attention. Overall, the high-dose B-complex formulation provided support in fulfilling their noted priorities, particularly those related to handling multiple exams, and having confidence to perform well. In addition, participants receiving the supplement claimed that it gave them better memory, improved their mental stamina and significantly improved their ability to focus. Overall, these results complement the evidence generated with the controlled interventional studies.

DISCUSSION

Healthy functioning of the CNS is known to depend on a wide range of micronutrients, particularly B and C vitamins, calcium, magnesium and zinc (1-5). Micronutrient deficiencies may arise from an imbalanced diet that does not satisfy micronutrient requirements, which can also be exacerbated by factors such as a stressful lifestyle, loss of sleep and missed meals (3,4).

Supplementation with multivitamins/minerals may improve mental and physical performance by replenishing levels of essential micronutrients that are not, or are insufficiently, consumed via the diet. Meta-analyses have presented consistent findings across a range of studies carried out in different countries that support the role of such supplementation in improving overall mood or aspects of mood (9,23). Currently available evidence has also suggested links between multivitamin supplementation, levels of blood micronutrients, homocysteine and C-reactive protein and clinical outcomes (1,4,19), which warrant further investigation. Our review indicates that the high-dose B-complex supplement Berocca is the most studied multivitamin formulation to date. Multiple double-blind, placebo-controlled RCTs that have specifically investigated this supplement demonstrate its beneficial effects on brain function and mental and physical performance (1,13,14,16-19). The supplement also led to significant improvements in fatigue, concentration, total mood disturbance and perceived stress, although not in all studies (13-15,18,19). Given its ease of administration and tolerability, which may be suggested by a compliance rate of at least 80 % in participants receiving the supplement (13,15,19), the potential for Berocca to restore micronutrient deficiencies not met through a balanced diet is promising, and offers a simple approach to promote optimal mental and physical performance in adults. In turn, improvements in mental

and physical energy would be expected to contribute to increased productivity, with associated economic benefits at a population level.

As detailed above, the breadth of results indicate that this supplement may be beneficial for mental and physical performance in healthy populations. However, it is recognised that not all research discussed is supportive of this, and further study of this topic is certainly warranted. It is important to recognise both the strengths and weaknesses that each presents with. For example, the inter-study variation due to the different methodologies and designs employed can be a barrier to the generalisability of findings. In particular, the studies considered different target populations, were generally limited in duration (≤ 33 days), and sample sizes were small and variable across studies (20-300 participants). In addition, some outcomes were only investigated in small participant subsets (16), and overall differences in the assessed outcomes across studies makes it challenging to draw comparisons and similarities between findings and make firm conclusions. Nevertheless, no serious adverse events were reported in any of the studies (if at all). Appropriate controls were performed where able, which included assessing or overseeing participant compliance with Berocca intake using a sensitive paradigm to assess treatment-related effects (serial 3s and serial 7s tasks), elimination of inter-individual variance, and minimising the possibility of type 1 errors (16,17). Moreover, studies employed a sensitive paradigm to assess treatment effect on differing cognitive facets; the serials 3s task can gauge psychomotor function, attention and working memory, while the serial 7s task can assess working memory and is better able to assess attentional and executive resources than the serial 3s task (14,16). Certainly, the use of clinically objective methodologies, such as fMRI for brain mapping, also constitute a strength of some of these studies, particularly as these appear to corroborate or supplement findings achieved with the objective questionnaires and CDB described above, which indicate improvements in mental performance. The role of high-dose B-

complex multivitamin/mineral supplementation in improving physical performance is a potential benefit that was not explored in the review by Maggini *et al.* (2). In this review, significant increases in self-reported physical vigour and stamina and protection from minor illness were revealed, which we believe may extend to potential improvements in physical performance.

Micronutrient deficiencies can be present in up to 50 % of some populations (4,6,7,24-28). Epidemiological data have shown an association between poor B-vitamin status and reduced cognitive function, which can be characterised by impaired energy metabolism in the brain, synthesis of neurotransmitters, and neuronal membrane ion pump and neuronal receptor binding (1-4,8). Evidence also suggests that B and C vitamins, calcium, magnesium, and zinc may be particularly important in supporting cognitive function (2-4), and low-normal concentrations of B vitamins (folate, vitamin B12 and vitamin B6) have arisen as candidate risk factors for both Alzheimer's disease and vascular dementia in the elderly (29). In addition, deficiencies in some B vitamins may have impact on physical parameters, by contributing to physical fatigue (2-4). Therefore, one might consider that the impact of micronutrient deficiencies can extend across different populations, and result in heterogenous, yet clinically relevant outcomes.

The influence of supplementation on the quality of life of populations has yet to be investigated. To address this, a large-scale, multi-country research was conducted to investigate how the intake of Berocca for 28 days impacts the daily quality of life of participants, with results showing increases in the perceived energy levels and feeling healthier as compared to before supplementation.

CONCLUSION

Given the prevalence of suboptimal micronutrient intake in people with poor diets and/or low micronutrient levels, even in otherwise healthy populations and developed geographies, there is a potential

application of a multivitamin/mineral supplement that can re-establish healthy micronutrient levels and provide specific neurochemical modulatory assistance in some instances. To our knowledge, the current formulation of Berocca is the most widely studied multivitamin/mineral to date, with the evidence demonstrating beneficial effects on cognitive performance and potential increase in physical energy levels. As detailed in this review, there is also a potential clinical application for use in the management of stress, anxiety, and mood.

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APPENDIX

Clinical study characteristics

Three questionnaires were used to assess mood, stress, general health, and mental and physical energy in the discussed clinical trials. These were 1) The General Health Questionnaire (GHQ) (13,14); 2) The Hospital Anxiety and Depression Scale (HADS) (13); and 3) The Profile of Mood States (POMS) scale (14,19).

GHQ is available in four different versions, is widely used for detecting general psychological health and distress, and is sensitive to short-term psychiatric disorders (30). The 12-item version (GHQ-12) is a very quick-to-administer questionnaire, which is used to assess the severity of non-psychotic and minor psychiatric disorders over the prior weeks. The 28-item version (GHQ-28) examines a profile of scores by considering four subscales of seven items each (somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression) (30).

HADS is a valid and reliable questionnaire, which can provide clinically meaningful psychological results (31). It covers seven items measuring anxiety and seven measuring depression, with each item scored on a 4-point Likert scale, and scores range from 0 to 21 for the anxiety and depression subscale (13).

POMS is a highly reliable, valid, and well-established measure of psychological distress. It consists of 65 items rated on a 0-4 scale across six mood states, described as “tension-anxiety”, “confusion-bewilderment”, “vigour-activity”, “anger-hostility”, “depression-dejection”, and “fatigue-inertia” (14).

Visual analogue scales (VAS)

Simple rating scales were used to assess anxiety, depression, tension, tiredness/fatigue, and ability to concentrate (14-16,19). The Perceived

Stress Scale-10 (PSS-10) is a widely used research tool with validity established in numerous participant populations.

Computerised cognitive assessments

The cognitive demand battery (CDB) was used to assess the impact of supplementation on speed/accuracy and mental fatigue during continuous performance of cognitively demanding tasks (14-16). The tasks included serial 3s (repeated subtraction of 3 from a randomly generated starting number) and serial 7s (subtraction of 7) in a repeated manner over a short period of time. This was followed by a rapid visual information processing (RVIP) task in which participants were asked to monitor a continuous series of digits for targets of three consecutive odd, or three consecutive even, digits. Following each repetition of the battery of tasks, participants rated their subjective feeling of mental tiredness. The usual 60-minute application of this battery has been shown to reliably measure participant self-ratings of 'mental fatigue' and to be sensitive to a number of nutritional interventions (14).

A mobile phone battery was used as an alternative to the CDB, and utilised JAVA™-enabled mobile phones instead to implement cognitive and mood assessments (15). This form of testing has been shown to be a sensitive method of assessing aspects of cognitive performance and delivering mood VAS. The testing package comprised fatigue and mood VAS (Bond-Lader mood scales, state/energy visual analogue scales), and was enabled for cognitive tasks ('arrow flankers' choice reaction time task, two-back working memory task).

Neuroimaging assessment of brain activity

Using fMRI techniques enables simultaneous capture of both behavioural data and brain activity with high spatial resolution that surpasses that of functional near-infrared spectroscopy (16,18). To our knowledge, the use of fMRI to specifically examine the effects of

vitamin supplementation on brain activation was first employed by Scholey et al, then in a further two studies (16-18). In these, fMRI techniques combined with in-scanner testing were used to investigate the effect of supplementation with Berocca on functional brain activation during higher-order cognitive functions (16-18). Brain scanning was implemented during RVIP and Inspection Time (IT) tasks, which assess different stages of information processing and attention; for example, the IT task assesses early information processing (16). To our knowledge, Berocca was the first multivitamin preparation to be studied for neurocognitive benefits using fMRI. Steady-state topography (SST) was used to explore fluctuations in the amplitude and phase of steady-state visually evoked potential (SSVEP) response during cognitive engagement using a task-irrelevant visual flicker. The narrow-band nature of the SSVEP offers important advantages over traditional electroencephalogram methods, including reduced susceptibility to noise contamination (17).

Table I. Short synthesis of the seven trials investigating supplementation with a high-dose vitamin B-complex multivitamin/mineral formulation (Berocca Performance, Bayer Consumer Health)

Reference	Study design	Patient population	Outcomes	Results
(13)	Randomised, double-blind, placebo-controlled trial <u>Treatment details</u> Treatment: • Berocca Performance • Placebo	• 80 healthy males • Aged 18-42 years	• Psychological wellbeing – GHQ-28 • Anxiety and depression – HADS, rating scales • Stress level – PSS, rating scales • Somatic symptoms –	**Post-treatment vs pre-treatment** **Berocca vs placebo** • Lower levels of anxiety and insomnia ($p < 0.08$) • Lower levels of anxiety and rated anxiety ($p \leq 0.05$) • Lower levels of stress ($p < 0.05$) • Increased concentration ($p = 0.07$)

	Duration: 28 days Dosage: once daily		physical symptom checklist	• Protection against minor illness (decreased somatic symptoms; $p < 0.05$)	
(14)	Randomised, double-blind, placebo-controlled, parallel-groups trial <u>Treatment details</u> Treatment: • Berocca Performance • Placebo Duration: 33 (± 2) days Dosage: once daily	• 215 healthy males • Aged 30-55 years • Full-time employed	• Mood – POMS • General mental health – GHQ-12 • Stress – PSS • Alertness, contentment, calmness – Bond-Lader mood scale • Fatigue – Energy VAS, Stroop task, executive functioning tasks (peg-and-ball task, Wisconsin card sort task) • Cognitive performance, mood and fatigue – CDB • Cognitive performance – arrow flankers choice reaction time task, two-back working memory task • Alertness, contentmen	**Post-treatment vs pre-treatment** **Berocca vs placebo** • Improvement in general mental health ($p < 0.05$)* • Lower subjective stress ($p < 0.05$) • Improvement in total self-rated POMS ratings ($p = 0.07$) • Improvement in self-reported POMS 'vigour' ratings ($p < 0.05$) • No significant effects on fatigue • Trend towards reduction in confusion levels ($p = 0.07$) • Reduction in mental tiredness ($p < 0.05$) • Trend towards improvement in mental fatigue ($p = 0.09$)	
(15)	Randomised, double-blind, placebo-controlled, parallel-groups trial <u>Treatment details</u> Treatment: • Berocca Performa	• 198 healthy males • Aged 30-55 years • Full-time employed		**Post-treatment vs pre-treatment** **Berocca vs placebo†** • Improved concentration ($p = 0.038$) • Improved mental stamina ($p = 0.04$) • Improved physical stamina ($p = 0.03$) • No significant differences between any groups on any	

		nce • Placebo Duration: 28 days Dosage: once daily		t, calmness – Bond-Lader mood scale • Stress, concentration, mental/physical stamina – VAS	cognitive performance outcomes
(16)	Randomised, double-blind, balanced, placebo-controlled, crossover design <u>Treatment details</u> Treatment: • Berocca Performance • Placebo Behavioural assessment: participants attended a practice visit on 1 day and completed assessments on 3 study days fMRI testing: participants were scanned during three separate one-hour sessions Dosage: once per study day	• 20 healthy females and males (behavioural assessment) • 5 additional enrolled in fMRI investigation • Aged 21-39 years	• Mood – VAMS • Anxiety – STAI-S • Bond-Lader mood scale • Stress – VAS • Mental fatigue – VAS • Cognitive performance – CDB, RVIP task • Brain activation – SST (n = 18), fMRI (n = 5)	**Berocca vs placebo** • Increased activation of right precentral gyrus, left and right cerebellum during an RVIP task ($p < 0.01$) • Negligible brain activation differences during an IT task
(19)	Randomised,	• 55	• Mood –	**Post-treatment vs pre-**

	placebo-controlled, double-blind parallel groups <u>Treatment details</u> Treatment: • Berocca Performance • Placebo Duration: 28 days Dosage: once daily	• healthy females and males • Aged 18-39 years	• POMS, PSS, VAS, STAI-S • Blood biomarkers • Cognitive performance – IT task, RVIP task, spatial working memory task, continuous performance task, SST (n = 40)	**treatment** **Berocca vs placebo** • Increased vitamin B6 ($p < 0.001$) and B12 ($p = 0.001$) levels • Non-significant increase in red cell folate ($p = 0.085$) • Reduced homocysteine ($p = 0.01$) • Lower depression/dejection ($p = 0.018$) • Lower stress ($p = 0.110$) • No significant effect on total mood disturbance ($p = 0.218$) • No significant effect on perceived stress ($p = 0.225$)
(18)	Randomised, double-blind, placebo-controlled design <u>Treatment details</u> Treatment: • Berocca Performance • Placebo Duration: 28 days Dosage: once daily	• 58 healthy females and males (16 completed SSVEP and fMRI assessments; 23 completed SSVEP alone; 16 completed fMRI alone)	• Functional brain activity – SSVEP recordings, fMRI	**Berocca vs placebo** • Increased functional activity in centro-parietal brain regions (related to processing of attention and working memory) during cognitive task performance ($p > 0.05$) • No differences in behavioural performance ($p > 0.05$)

		• Aged 18-40 years		
(17)	Randomised, double-blind, placebo-controlled, three-arm, balanced crossover design <u>Treatment details</u> Treatment: • Berocca Performance • Placebo Participants attended a practice visit on 1 day and completed assessments on 3 study days Dosage: once per study day	• 20 healthy females and males • Aged 21-39 years	• Functional brain activity – SSVEP while completing cognitive tasks (A-X CPT)	**Berocca vs placebo** • Increased brain activation in key task-related brain regions during the hold and target segments of the A-X CPT, which reached significance on some electrodes at the first visit o Pattern of further frontal amplitude reduction and phase advance (latency reduction during the hold segment) ($p < 0.01$) o Pattern of frontal SSVEP amplitude reduction and prefrontal SSVEP phase advance persisted into the target segment, with marginal significance ($p < 0.05$), with a single right frontal

	electrode site reaching significance

*ANCOVA including additional fruit/vegetable consumption covariate. †Significance was reached during post-work assessments, except for physical stamina, where significance was reached across both pre- and post-work assessments. ANCOVA: analysis of covariance; A-X CPT: A-X continuous performance task; CDB: cognitive demand battery; fMRI: functional magnetic resonance imaging; GHQ: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; IT: Inspection Time; POMS: Profile of Mood States; PSS: Perceived Stress Scale; RVIP: rapid visual information processing; SST: steady-state topography; SSVEP: steady-state visual evoked potential; STAI-S: State-Trait Anxiety Inventory – State Portion; VAMS: visual analogue mood scales; VAS: visual analogue scale.

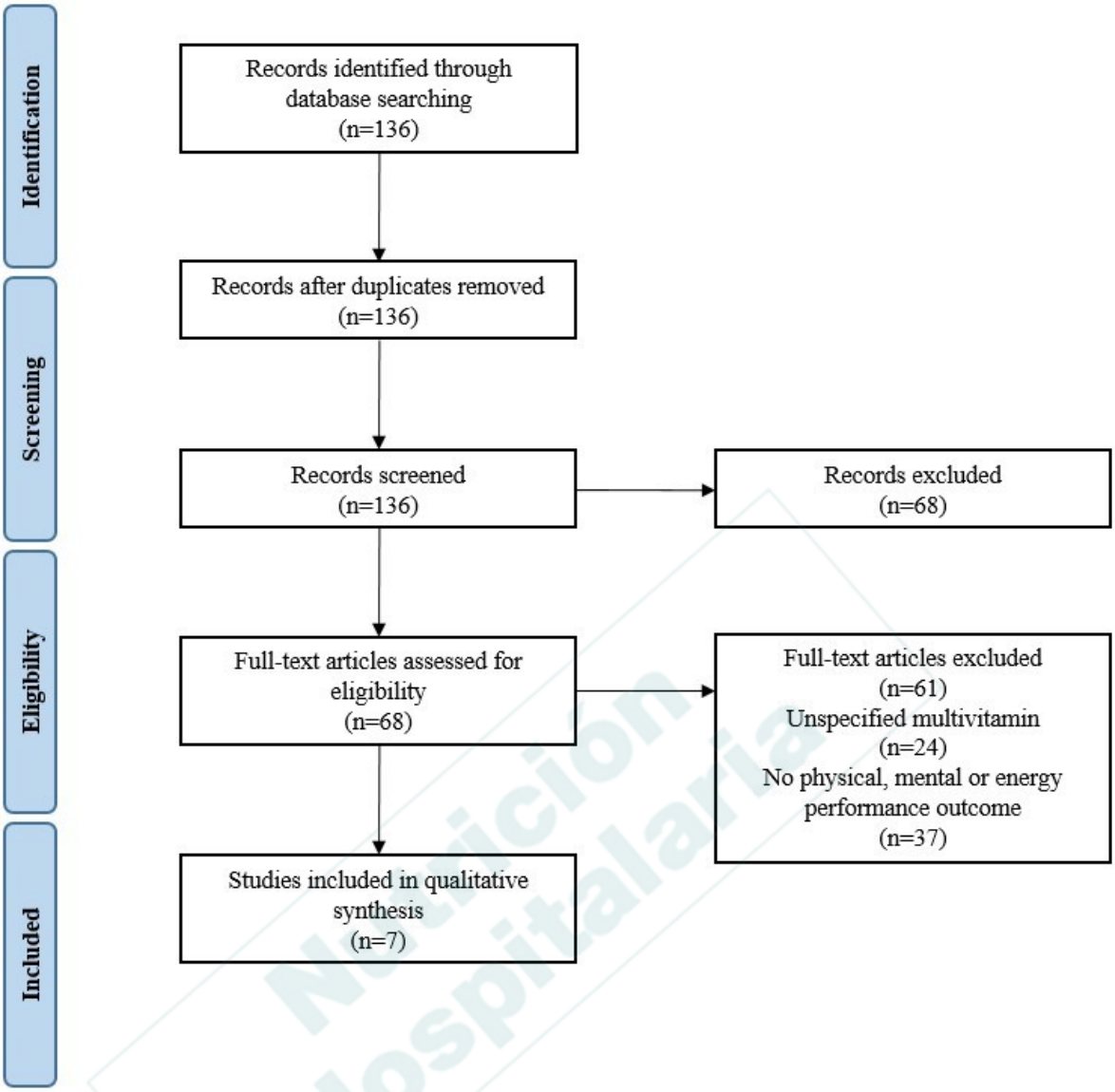

Fig. 1. Flow diagram depicting the selection process for the articles analysed in this review.

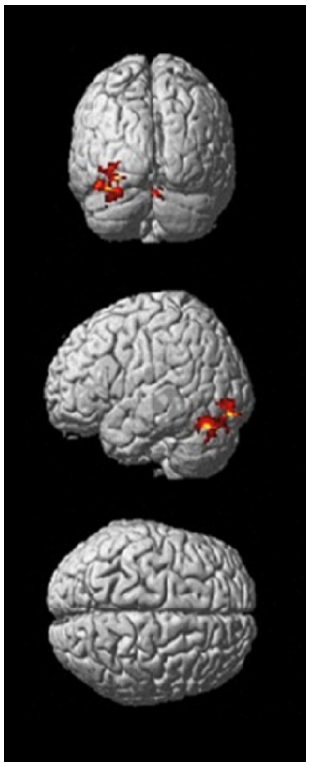

Fig. 2. Brain activation patterns associated with supplementation with the high-dose vitamin B-complex multivitamin/mineral formulation (Berocca Performance, Bayer Consumer Health) compared with placebo during the rapid visual information processing (RVIP) task. Posterior (top panel) and left lateral surface (middle panel) and dorsal (bottom panel) views of brain surfaces showing significantly greater activation during the RVIP task for Berocca Performance compared with placebo ($p < 0.01$) (16). Figure adapted from Scholey et al., 2013 (DOI: 10.3390/nu5093589; open access article distributed under the terms and conditions of the Creative Commons Attribution license).

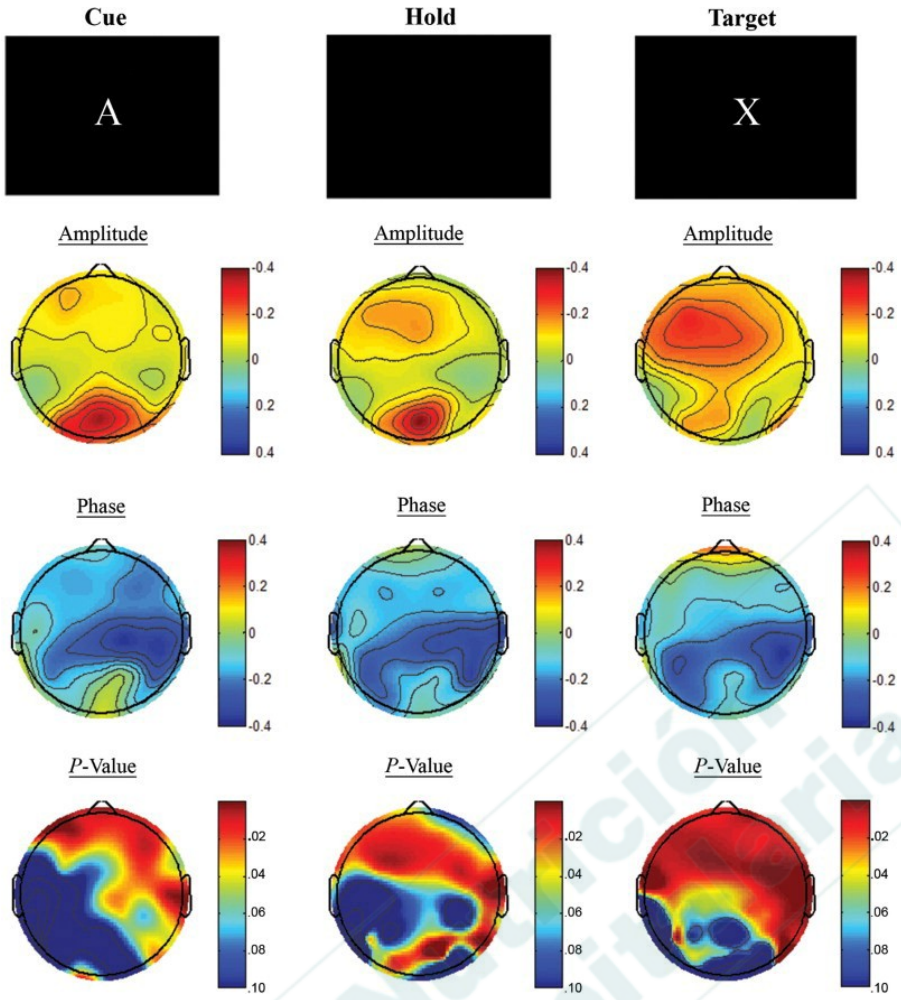

Fig. 3. Topographic maps of differences in steady-state visual evoked potential (SSVEP) amplitude and phase for the A-X continuous performance task (A-X CPT) at the supplementation (Berocca Performance, Bayer Consumer Health) and placebo visit. Each column shows topographic maps of SSVEP amplitude and phase differences with supplementation versus placebo, with the bottom map showing the p-values resulting from the Hotelling's T2 contrast of the two treatments. Warm colours indicate amplitude and latency reductions (phase advance) and lower p-values, respectively, and cool colours represent amplitude increases and latency increases (phase lag). Supplementation was associated with a pattern of frontal SSVEP amplitude reduction and phase advance during the hold ($p < 0.01$) and target ($p < 0.05$) segment of the A-X CPT (17). Figure obtained from White et al., 2017 (DOI:

10.1179/1476830514Y.0000000157; permission not required for use in this publication).