THE ESSENTIALS OF A GLOBAL INDEX FOR COGNITIVE FUNCTION

Abstract

Cognition is comprised of the faculties: perception, creativity, intuition, and ratiocination. Optimal levels of cognition are needed for independent functioning and balanced living. With an aging population that continues to grow, dietary supplements that tilt the balance towards maintenance of cognition are being marketed for vulnerable populations facing these challenges. Randomized clinical trials provide the causal inference necessary to define the efficacy of emerging nutraceuticals. Cognition testing, in particular, requires a battery of tests that encompass all brain regions involved in cognition so as to provide endpoints necessary for product validation. The lack of well controlled studies for comparison analyses, limited sample sizes, ambiguous dosages, and poor cognitive measures result in data that cannot be compared across studies to determine the efficacy of supplements claiming to enhance cognition. Clinical trials for the nutraceutical industry should consider the multifaceted nature of supplements, where clinical endpoints must be comprehensive while remaining feasible. Combining endpoints of cognition with physiological biomarkers of immunity and metabolism to arrive at a global index for cognitive health may be necessary for claim substantiation in order to fully justify and scientifically validate improvements in cognitive health. The issues and needs of a global index will be discussed here.

Keywords

• Cognition • Dietary Supplements • Neuropsychological Tests • Global Index

The complexity of defining good cognitive health

Cognition is the ability to think, learn and remember, thus forming the basis for an individual’s capacity for perception, reasoning, acts of creativity, problem solving and possibly intuition [1]. Good cognitive health, particularly during aging, is integral to maintaining independence and staying active. While modest age-related declines in cognition and memory are normal, health problems underlying these symptoms can raise concerns necessitating interventions. Approximately 30 million adults, the majority of who are men under the age of 50 years, take supplements for brain health [2]. Consequently, there is a need to understand whether existing tools and biomarkers can confidently support the efficacy of nootropics in the nutraceutical industry. As it pertains to mental health, many major psychiatric disorders have reliable indicators in depression, stress, burnout, panic disorders, etc. [3], making it easier to define the absence of mental disorders. Conversely, defining ‘good cognitive health’ provides a bigger challenge as it is not immediately clear what contributes to good/optimal cognitive health, demonstrating the fact that it is easier to screen for the presence of disease rather than the absence of it. The aim of this brief review is to elucidate the essentials of a global index by creating a single composite endpoint based on cognitive, immune, physiological and emotional markers.

Current modes for measuring cognitive health

While pharmaceutical management of cognition mostly targets dementia related to ageing and disease, nutraceutical modulation aims to maintain cognition and prevent cognitive decline in healthy individuals. The impact of probiotics on mood has been demonstrated in clinical studies [4] with gut microbiota dysbiosis having been hypothesized to affect cognitive function [5]. A variety of phytochemicals including resveratrol, green tea extract, beta carotene, as well as chromium picolinate and antioxidants have supporting clinical evidence that demonstrates improvements in cognition (Figure 1).

Clinical trials evaluating the efficacy of dietary supplements embrace tools that measure cognitive functions, but are only useful if they encompass all aspects related to the polyvalent nature of nutrients. This is exemplified by clinical trials evaluating the efficacy of nutrients having mostly utilized the mini mental state examination (MMSE) as an outcome measure of cognitive performance, when in actuality this is a measure of cognitive impairment. As nutritional effects are generally subtle, the application of tests that measure degree of impairment when evaluating performance in an un-impaired population is highly questionable as this method will most likely not capture sufficient variability in performance scores to...
facilitate the detection of subtle effects [6]. Additionally, adult participants in nutrition studies who are cognitively unimpaired fall within a range in several demographic features that likely have an impact on the efficacy of the nutrient intervention used. For example, race was directly associated with cognitive functioning and indirectly associated through social risk factors such as education and health insurance [7], thereby influencing the outcome of cognitive testing, it is therefore necessary for study design to be cognizant of these variables. Inclusion/exclusion criteria must allow for screening of individuals presenting a genetic risk of cognitive decline, identified through polymorphisms in Brain-Derived Neurotrophic Factor (BDNF), Catechol-O-methyltransferase (COMT) and Apolipoprotein (APOE) genes [8], or contrariwise presenting a genetic advantage in cognition tests, identified through increased levels of the Klotho gene variant [9].

Inconsistencies in results obtained using MMSE as a tool to detect meaningful differences in cognitive function in nutrition studies have been noted. Further, the pervasive use of MMSE in clinical trials evaluating dietary supplements that assess cognition have mostly included patients with various cognitive impairments, resulting in a lack of studies showing a direct comparison between supplements. For example, two years of supplementation with folic acid and vitamin B_{12} did not affect cognitive performance in 2919 elderly participants with elevated homocysteine levels [10]. In contrast, elderly individuals suffering from chronic fatigue syndrome showed a significant improvement in MMSE score after supplementation with acetyl L-carnitine compared to a placebo (3.4 vs. 0.5 respectively) [11]. Corroborating the aforementioned finding are the results of a longitudinal study of healthy individuals where the cognitive state of a cross-sectional sample was analyzed in response to consumption of fruits and vegetables. Here, the MMSE used as a measure of global cognitive function uncovered an effect of diet on cognition [12].

**Randomized Controlled Trials in Clinical Nutrition**

The gold standard for scientific evidence is the randomized controlled trial (RCT), which has been unequivocally accepted in order to make valid health claims in the nutraceutical and pharmaceutical industries. However, the design of a clinical trial should be subject to the product being tested. Pharmaceutical drugs
The tests were not readily comparable, the were of limited use under study conditions, susceptibility to change over time and thus their sensitivity to nutrient interventions or studies, it was revealed that the cognitive tests this population. On further dissection of these several other domains of cognitive function in attention and concentration but not any of supplementation in older children and adults systematic review and meta-analysis of oral iron attributed to the choice of cognitive enhancing cognition function have been investigating the potential of nutrients to nutritionally adequate, thereby reducing the effect size. This reflects a major problem with RCTs designed to demonstrate clinical evidence for nutrients in cognition and in general health. Due to the inherent challenges with study designs that do not factor in the baseline nutrient values of a population such that the responder population may be facing inadequate levels of a nutrient [13], there is a need for a better approach that generates sufficient contrast in outcomes between control and supplementation with nutrients.

Neuropsychological Tests in Nutrition Research

Negative findings from clinical trials investigating the potential of nutrients to enhance cognition function have been attributed to the choice of cognitive neuropsychological tests used in the trials [14]. A systematic review and meta-analysis of oral iron supplementation in older children and adults revealed that iron supplementation improved attention and concentration but not any of several other domains of cognitive function in this population. On further dissection of these studies, it was revealed that the cognitive tests employed were not necessarily selected for their sensitivity to nutrient interventions or susceptibility to change over time and thus were of limited use under study conditions. The tests were not readily comparable, the accuracy and error rates were not provided and the reproducibility, validity and adoption of cultural and language-sensitive issues related to the tests were not considered [1].

Non-verbal intelligence, normally assessed in children in nutritional intervention studies, have generally used internationally recognized culture-fair tests such as Raven’s Colour Progressive Matrices and Comprehensive Test of Non-verbal Intelligence [15]. Application of these cognition tests to evaluate micronutrient supplementation in children aged 5-15 years did not demonstrate a consistent impact on intelligence and long-term mental functions [15]. However, food fortified with multiple micronutrients enhanced short-term memory in this population, perhaps through a synergistic role affecting the hippocampus that regulates information encoding and retrieval for short-term memories [15].

The need for a battery of tests

Cognitive measurement techniques in clinical trials for the nutrition industry provide varying responses that depend on the test population, the dietary supplement, trial design and the neuropsychological test. Therefore, obtaining conclusive results on the efficacy of the supplement or nutrient is proving to be challenging. The requirement that claims substantiation must be made only on healthy individuals for the dietary supplement industry has further restricted study inclusion and exclusion criteria, causing improvements in cognition in a healthy population to be a demanding task. Assessment of cognition using estimates of verbal intelligence and symbol search were found to be less sensitive to the subtle effects of dietary supplements [16], and therefore computerized measures of fluid intelligence were proposed as a more responsive measure of the cognitive enhancing effects of dietary supplements [14].

It may be postulated that a battery of tests to complement the MMSE are needed to differentiate between the nuances of cognition testing. However, RCTs employing such a strategy were found to have limited success in efficacy studies. A meta-analysis of 17 RCTs found no significant difference in cognitive function between participants who supplemented with B vitamins and placebo, regardless of the duration of the study or the battery of cognitive tests used [17]. Similar results have been reported after supplementation with eicosapentaenoic acid and docosahexaenoic acid for 26 weeks in 302 cognitively healthy individuals aged 65 years or older and subjected to a battery of neuropsychological tests [18]. Cognitive functions measured by Continuous Attention Test, Four-Choice Reaction Time, Digit-Symbol Substitution and Scanning Memory Sets in 24 healthy elderly subjects (73 ± 5.6 years) supplemented with folic acid for four weeks did not show any enhancement in cognition [19]. Rey Auditory Verbal Learning Test (RAVLT) captures an individual’s ability to encode, combine, store and recover verbal information in different stages of immediate memory. The process of administering this test is meant to demonstrate the ability to retain information despite the intervening activity and distinguishes problems associated with registration and storage from those of inefficient recall [20].

Cognitive function measured by a battery of tests including MMSE memory, RAVLT, immediate recall, delayed recall, and recognition, digit span forward and reverse, doors test, complex attention tasks, digit symbol substitution and trail making, A1, A2, and B, verbal skills, verbal fluency A and N, animals and occupations, and the Boston Naming Task in 202 healthy post-menopausal women aged 60-75 years showed that supplementation with soy protein containing isoflavones did not improve cognition [21].

Contradicting these findings is the observation that there was a significant effect of age, time, and treatment (vitamins and placebo) in RAVLT, showing a positive effect on some measures of memory performance in 211 healthy young, middle-aged and older women after short-term supplementation with a formula of folate (750 µg), vitamin B₆, (15 µg), vitamin B₉ (75 mg) or a placebo. No difference in speed of processing was observed but measures of memory evaluating recognition showed an effect of age, time and time x age x treatment. Evaluation of executive function revealed a significant effect of age, time and
time x treatment only in the initial letter test of verbal fluency. There was little evidence of positive effects after administration of short-term vitamin B supplementation and statistical analyses did not show whether differences observed were between supplementation and placebo [6].

Since presumably similar tests, conducted on different populations and dietary supplements, yielded contrasting results on cognition, reaching a consensus on a particular test or a battery of tests is proving to be difficult. In this respect, the Swinburne University Computerized Cognitive Assessment Battery (SUCCAB) that assesses cognitive functions such as information processing speed, attention and memory has been shown to be sensitive to subtle changes in cognitive performance following certain nutraceutical interventions [14, 22, 23]. Others have used SUCCAB to capture improvements in processing speed and visual working memory after cognitive training [24] and testing neurocognitive effects of phospholipids [25]. Yet, when participants were supplemented with a different formulation, SUCCAB failed to show a difference [26], perhaps due to the choice of placebo used, or indicating the need for further validation of SUCCAB in various populations, interventions and in the presence of confounders.

Complementing these tools is the Cognitive Drug Research Computerized Assessment Battery (CDRCAB) that has been used in several drug trials and has also found its way into clinical trials evaluating the efficacy of dietary supplements. For instance, CDRCAB detected significant improvement in the accuracy of memory task performance, secondary memory and speed of memory after acute oral administration of essential oil from the Spanish sage, Salvia lavandulaefolia, in comparison to the sunflower oil placebo. Secondary memory incorporates elements of learning, consolidation and retrieval of episodic information, while speed of memory specifically reflects retrieval efficiency [27].

In order to avoid underestimating declines with normal ageing, neuropsychological tests have to assess speed and accuracy of performance [28]. Crucially, these studies combined cognitive measures with a subjective measure of mood and were able to demonstrate not only enhanced cognition but also a better mood experienced by participants after supplementation, likely through induction of estrogens [29]. In essence, this study captured a gamut of endpoints and was able to show that supplementation with essential oils had multifaceted effects that is typical of dietary supplements. Others have shown the validity of CDRCAB for testing the efficacy of ginseng [30], milk fortified with modified sucrose and lactose [31] and rosemary (Rosmarinus officinalis L.) [32], indicating that while CDRCAB has been widely used in drug trials, aspects of this tool can be adapted to the nutraceutical industry.

The Computerized Mental Performance Assessment System (COMPASS) has been used in several nutritional intervention studies [33-35] and was found to be sensitive to cognitive enhancement following supplementation [36]. For example, in a study on healthy males, a high dose vitamin B complex with mineral supplement showed a significant enhancement in the COMPASS Serial 3s subtraction task, an attention domain in cognition, and also boosted mental energy among participants [37]. A pilot study likewise showed improvement in working memory that was evaluated using COMPASS [38].

As mentioned earlier, MMSE suffers from an inability to detect subtle changes in cognition. In fact, at 90% sensitivity for discriminating patients with mild cognitive impairment from healthy controls, the specificity ranged between 65 – 85%. Again, when discriminating between patients with dementia from healthy controls, at a sensitivity of 90%, the specificity ranged between 50 and 81%. Therefore, as most cognition testing tools lack the predictive power to discriminate between those with mild impairment and those with more advanced cognitive decline, it is not surprising that if artificially set at 90% sensitivity, the specificity to discriminate between improved cognition with dietary supplements in an healthy population may be predicted to be poor as well.

Though SUCCAB, CDRCAB and COMPASS captured subtle changes in cognitive performance in some studies, it is plausible that relying entirely on cognitive domains but ignoring a wide range of psychological (mood, health and dietary habits), cardiovascular (brachial pressures, aortic pressures and carotid-femoral pulse wave velocity), biochemical (HbA1c, insulin, cytokines) and genetic (APOE4 allele, polymorphisms in BDNF and cytokines) measures [39], may not reveal the efficacy of the investigational product in maintaining or improving cognitive performance.

Summarising evidence gathered from various cognitive tests that are sensitive to subtle changes to nutritional interventions in healthy adults, the broader domains of Input (Attention-Reaction Time), Storage (Memory-Recognition), and Control (Executive Function and Decision Making-Spatial Working Memory) can specifically be altered by dietary and nutritional supplements and may form the core of endpoints likely to change in healthy individuals.

These findings suggest that unless a comprehensive set of primary endpoints are developed, contradictions and inconsistencies in efficacy reporting of dietary supplements will lead to inconclusive results such that individuals who are at risk of disease may be unwilling to adopt medications that they believe may either put them at risk or are simply ineffective [40]. This notion may also be true for healthy individuals who may be reluctant to adopt dietary supplementation to delay or prevent age-related cognitive decline. It is therefore essential for clinical studies aimed at improving cognitive health to approach the issue of primary endpoints with caution, placing focus on the goal of identifying optimal endpoints that give the best chance at detecting a positive outcome. This may be captured using a global index for cognitive health.

A Global Index for Cognitive Health

Global indices of health may be appropriate in the dietary supplements realm since functional foods and dietary supplements do not follow the pharmaceutical model where a global index in the form of composite endpoints may be used for statistical convenience and not to solve a medical problem. In clinical trials that evaluate the efficacy of a drug, use of a global index comprising multiple single endpoints to
improve statistical precision, increase efficiency, reduce trial size, cost, and to obtain trial results earlier is warranted. These endpoints may be clinically relevant outcomes of validated biomarkers or surrogates and are currently widely used in cancer chemotherapy [41], cardiovascular disease [42] and rheumatoid arthritis [43].

The dietary supplement industry currently faces challenges from structure/function and other claim substantiations that are the targets of regulatory bodies. The efficacy of dietary supplements is subject to trial design and chosen clinical endpoints. Clinical trials in the nutrition industry are subject to the same rules as the pharmaceutical arena, even though fundamentally, the former follows a holistic approach for prevention of disease and health promotion, while drugs target a specific biochemical or signaling or a pathway in a disease.

On the corollary, choosing validated clinical endpoints for a healthy population is fraught with complexities including the type and absolute levels of biomarkers in a healthy population such as plasma cytokines, blood count, urine metabolites, that are less understood at least in terms of their profile in health. In the absence of population baseline data for nutrient levels, the efficacy of dietary supplements is subject to a responder population and therefore, there is a need to distinguish between a flawed trial design, poor sensitivity of the clinical endpoints and an ineffective investigational product.

In the case of neurological health, particularly cognitive improvement through nutrition, identifying a global index for cognitive health that reflects health rather than disease and is tailored to the unique features of nutrients actions and interactions may help overcome the design problems that have resulted in a growing number of failed trials of individual nutrients [44]. A global index may be a primary endpoint for studies to determine the effect of nutrients on cognition. For example, there is good evidence that suggests vitamin E plays a role in treating cognitive decline or dementia. In a large prospective cohort study comprising 5395 participants (> 55 years) who were followed for over 9.6 years, high intake of vitamin E-rich foods was found to modestly reduce development of dementia by 25% compared to those with the lowest intake of vitamin E [45]. Vitamin E has an effect as an antioxidant playing a key role in protecting membranes from oxidation, peroxidation of docosahexaenoic acid in the brain, and reducing the risk of mild cognitive impairment by 15% in people with the highest levels of tocopherols and by 8% in the case of tocotrienols [46]. Vitamin E, in addition to being an antioxidant, is also involved in immune functions, metabolism, blood flow and a host of other physiological processes.

A global index that encompasses all these outcomes and sums the effects of a nutrient across systems corresponds more closely to the action of nutrients in the human body than any single-system outcome measure. It also provides a higher power to more ably detect small changes across multiple organ systems, changes that may be otherwise difficult to detect by simply investigating one organ system. A global index may help to pinpoint systems that show clinical improvement [44] by capturing appreciable changes in the responder populations through combining multiple endpoints, in turn reducing the non-responder population of a given cohort and improving the likelihood of detecting a positive effect.

Variations between patients in the progress of a cognitive disease such as dementia are a reflection of the complexities of the brain, where several different cell types, brain regions and pathogenic processes act in independent ways resulting in dementia. Similarly, individual variation exists in a healthy population due to genetic, epigenetic and microbiome differences, which dictate the response to a nutraceutical intervention and in turn endpoints that are sensitive to these changes are required to form a global index. A single endpoint measuring memory for instance, might not capture the effect of the nutraceutical intervention in all participants. Hence, combining endpoints that reflect memory, executive function and language could capture cognitive enhancements more completely.

The rationale for a global index encompassing multiple endpoints that incorporates physiological, immunological and biochemical markers is a systems biology approach to studying outcomes. This is particularly evident in the case of cognitive functions that should not be thought of solely in terms of the nervous system, but also that environmentally linked changes in brain architecture continue throughout the lifespan, due to the plasticity of the brain [47]. An important environmental variable to consider in relation to brain function is, as was previously mentioned, nutrition [47]. Nutrition is known to be a relevant effector of health and disease [48], with contributions from the immune [49] and vascular systems [50].

Pooling and measuring biomarkers of cognitive health such as executive function, memory, attention etc. to arrive at a global index that evaluates and quantifies cognitive health may include, quality of life questionnaires, the medical history of the participant, physical examination, laboratory tests and imaging studies [51], that are correlated and not independent of each other. Incorporating cognition, immunity, metabolism and psychological functions into this global index may be meaningful for dietary supplements with multifaceted effects. For example, supplementation with a blend of phytochemicals and choline, altered epidermal growth factor (EGF), an immune function marker, along with improvements in cognition [52]. Supplementation with omega-3 fatty acids enhanced cognition and cerebral blood flow, particularly in the prefrontal cortex, in comparison to the placebo assessed by near-infrared spectroscopy during cognition testing [53]. Supplementation with extracts from French Pine Bark showed a significant reduction in oxidative stress, measured as free radicals in plasma, with a significant improvement in cognitive function [54].

Quality of life that measures good/optimal health reflecting subjective well being or happiness and captured through tools such as the Oxford Happiness Questionnaire [55] and the Bhutan Happiness Index (www.grossnationalhappiness.com) should also comprise the global index. This human trait has not been captured in clinical trials evaluating dietary supplements, despite happiness being
the outcome of multiple emotional factors, triggered by various biological endpoints that are known to be affected in a multi-layered paradigm exerted by dietary supplements. Thus, immune markers, blood flow, oxidative stress and happiness may be surmised to comprise a global index for cognitive health (Figure 2).

It would therefore be imperative to identify a global index comprising multiple endpoints that encompass global indices of cognition, particularly executive function and memory, using tools such as RAVLT, CDRCAB and SUCCAB excluding N-back, visual vigilance and word recall tasks (Andrew Pipingas, personal communication) that have been proven to be adaptable to the nutraceutical industry. Combining these tools with Oxford Happiness Questionnaire and Bhutan Happiness Index, along with understanding the study population as described earlier [51] must be a priority for validation in clinical trials.

Epidemiological studies have not been very productive in identifying blood, saliva, urine or cerebrospinal fluid (CSF) markers associated with optimal cognition in a healthy population, although screening an entire gamut of metabolites, including those related to neurotransmission, is being adopted in mainstream clinical research. Alternatively, characterization of nutrient response patterns along with indices of brain health derived from high-resolution magnetic resonance imaging (MRI) [56] may serve as useful surrogate markers of cognition enhancement through dietary supplements. This has been demonstrated in healthy adults subjected to cognitive testing using near infra-red spectroscopy and electroencephalography after supplementation with krill oil [57] and by means of functional MRI after supplementation with fish oil [58].

To design a statistically valid and practically feasible approach to dealing with the variations commonly seen in cognitive research due to the large number of variables, a relatively simple approach is to combine tests that measure comparable items into composites, such that when multiple related tests are performed, a composite ability factor can be derived. In order to decide the variables that should form composites, it would be ideal to combine variables that are correlated to each other ($r > 0.5$), which would indicate that the subset measures a common factor. Running a factor analysis or principal component analysis would be a sophisticated approach to achieving this, though factor analysis may not be possible if the sample size is small.

The aim of this brief review is to identify the essentials of a global index necessary to creating a single composite measure based on cognitive, immune, physiological and emotional markers. The individual tests relate to cognition and therefore there is precedence for grouping tests, which is evident in the form of batteries of tests to evaluate cognitive function. To develop a composite score, the factor saved score, where factor analysis allows calculation of its own composites, or the weighted composite can be used. The latter involves designing a linear composite of the component variables. The component variables can be combined into a composite using a simple procedure such that composite equals the sum of all test scores. By simplifying the complexity of the data and presenting it in a more sparing manner the composites can be used in subsequent analyses such as predictors in regressions, dependent variables in group comparisons etc. [59, 60].

Cog-GI (Cognitive Global Index), proposed here, describes the use of several outcomes for a global index based on capturing individual responses to an intervention. The Cog-GI may be developed using a score that includes other variables depending on the ingredients studied. Variables that are correlated to cognition include levels of EGF, cerebral blood flow, plasma free radicals and Oxford Happiness Index. The goal being a shift from a singleton endpoint capturing the outcome predicated on a one-drug-one disease concept to one that is more encompassing of several outcomes [13, 44]. Moreover, while the notion of a global index is appealing in its relative simplicity and feasibility, creating the Cog-GI is possible through other means. For example, machine learning techniques, including support vector machines that combine very large and disparate data sets that are divided into two groups - one to train the machine and the other to test the machine [61]. Though this technique can discriminate between cognitive impairment and cognitive sufficiency, it may...
not be useful for defining improvements to standard biomarkers and may be impractical for applications in multi-site clinical trials.

The rationale for studying and presenting this work is not only to highlight the specific potential value of combining these variables, but to suggest a simple approach for combining disparate sets of data to create a global index that is of higher relevance. A global index will not only create stronger correlations with known functional measures in a cross-sectional fashion, but also to provide better outcomes longitudinally with the goal being to identify and track cognition improvement than single tests alone.

When combining data sets, there is the potential to increase noise in the longitudinal data set since each test variable has its own associated variability. It will therefore be essential to investigate longitudinal analysis as well as determining whether such composite measures are truly valuable in clinical trials involving investigation of cognition in healthy people and this concept should be tested further in a prospective fashion. As clinical longitudinal trials result in an abundance of competing data sets, how combinations of other measures obtained from these studies can improve upon individual parameters need to be investigated.

Composite scores such as the NIH Toolbox Cognitive Function Battery have been developed to reliably measure important aspects of cognition in children between the ages of 3 and 15 [62], or for use in patients suffering from Alzheimer’s disease [63] but noticeably absent in clinical trials evaluating dietary supplements. Generally, tools developed for diseases and pharmaceutical drug evaluation are adapted for use in the dietary supplement industry. The NIH Toolbox required rigorous work examining the psychometrics of the test battery in large clinical populations before being used as primary outcomes in clinical trials [64]. The lack of discriminant validity for some of the measures indicates either a weakness in measurement specificity or in the case of children where this was used, a developmentally appropriate lack of differentiation of cognitive skills [64]. This suggests that NIH Toolbox requires further validation for pharmacological applications and for the dietary supplement industry. A battery of tests to evaluate cognitive function is likely to show a difference between drug and a placebo versus a dietary supplement and a placebo due to the multi-faceted nature of nutrients that act on multiple targets in a healthy individual and the specific nature of drugs that act on a single target in the context of a disease. Therefore, cognition testing tools will be effective when employed in a diseased population compared to healthy individuals who adopt dietary supplements to prevent disease or maintain their health.

The use of global indices is not without precedence. Clinical composite measures such as DAS28, CDAI, SDAI or questionnaires such as RAPID3, RAID and PRO-CLARA allow physicians to easily and rapidly quantify rheumatoid arthritis disease activity levels and patient responses to therapy and provide a comprehensive understanding of the patient’s progress [43]. As conceptual overlap of study designs from the pharmaceutical realm into the nutraceutical industry has strengthened evaluation of safety and efficacy of dietary supplements, identification of a global index for cognition may be justified based on fundamental differences between the polyclavent action of nutrients and the disease-specific drug model.

In a departure from the standard RCT, an Augmented RCT® for the dietary supplement industry has been proposed previously [65-67]. This two-stage design would first test an intervention in an open label study followed by a correlation analysis on subgroups that respond to the intervention or by a meta-analysis of several N-of-1 studies encompassing numerous participants. Information gathered from the first stage pertaining to outcomes, responders and level of efficacy will be used in RCTs as inclusion criteria and in building a global health index to quantify outcomes. This augmented design is more conducive to capturing efficacy of dietary supplements, which have multifaceted effects and overcome the limitations of the gold standard RCT that preferentially favors the objectives of pharmaceutical trials over dietary supplement trials [65-67].

Conclusions

RCTs evaluating dietary supplements generally use MMSE to determine the outcome of cognition testing in a healthy population. Due to the inherent weakness of using MMSE in a clinically healthy population, there has been a shift towards use of computerized battery of tests that have been validated to identify the subtle differences experienced with the use of dietary supplements. Evidence indicates that tests detecting subtle differences exerted by dietary supplements offer better and validated alternatives to test cognition. Composite endpoints identified from tests of cognition, together with physiological, psychological and emotional biomarkers that can be influenced by nutrients and efficacy studies should comprise a global index, which must be validated in RCTs for the dietary supplement industry. It is plausible that combining endpoints to form a global index will help in scientifically validating claims to provide accurate science behind supplements and to meet the regulatory requirements for their substantiation.

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References

[1] Falkingham M., Abdelhamid A., Curtis P., Fairweather-Tait S., Dye L., Hooper L., The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis, Nutr J, 2010, 9, 4

[2] Olivo O, “Nutraceuticals to Nourish the Mind,” 2015.

[3] APA, Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association (APA), 2013

[4] Steenbergen L., Sellaro R., van Hemert S., Bosch J.A., Colzato L.S., A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood, Brain Behav Immun, 2015, 48, 258-264

[5] Guernier V., Brennan B., Yakob L., Milinovich G., Clements A.C., Soares Magalhaes R.J., Gut microbiota disturbance during helminth infection: can it affect cognition and behaviour of children?, BMC Infect Dis, 2017, 17, 58

[6] Bryan J., Calvaresi E., Hughes D., Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages, J Nutr, 2002, 132, 1345-1356

[7] Zsembik B.A., Peek M.K., Race differences in cognitive functioning among older adults, J Gerontol B Psychol Sci Soc Sci, 2001, 56, S266-274

[8] Wollam M.E., Weinstein A.M., Saxton J.A., Morrow L., Snitz B., Fowler J.A., Zsembik B.A., Peek M.K., Race differences in cognitive functioning among older adults, Br J Nutr, 2013, 109, 503-510

[9] Dubal D.B., Yokoyama J.S., Zhu L., Broestl L., Wang D., et al., A preliminary study on the effects of single versus multi-domain training, Transl Neurosci, 2015, 6, 13-19

[10] van der Zwaluw N.L., Dhonukshe-Rutten R.A., van de Rest O., Geleijnse J.M., Kok F.J., van Staveren W.A., Dullemeijer C., Olderikkerk M.G., et al., Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial, Neurology, 2008, 71, 430-438

[11] Health Quality O, Vitamin B12 and cognitive function: an evidence-based analysis, Ont Health Technol Assess Ser, 2013, 13, 1-45

[12] van de Rest O., Geleijnse J.M., Kok F.J., van Staveren W.A., Dullemeijer C., Olderikkerk M.G., et al., Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial, Neurology, 2008, 71, 430-438

[13] Pathansali R., Mangoni A.A., Creagh-Brown B., Lan Z.C., Ngow G.L., Yuan X.F., et al., Effects of folate acid supplementation on psychomotor performance and hemorheology in healthy elderly subjects, Arch Gerontol Geriatr, 2006, 43, 127-137

[14] Harris E., Macpherson H., Vitetta L., Kirk J., Sali A., Pipingas A., Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial, Hum Psychopharmacol, 2012, 27, 370-377

[15] Pipingas A. H.E., Tournier E, King R, Kras M, and Stough C.K., Assessing the efficacy of nutraceutical interventions on cognitive functioning in the elderly, Current Topics in Nutraceutical Research, 2010, 8, 79-87

[16] Walker C.C., Kavanagh A., Downey L.A., Lomas J., Camfield D.A., Stough C., Online cognitive training in healthy older adults: a preliminary study on the effects of single versus multi-domain training, Transl Neurosci, 2015, 6, 13-19

[17] Scholey A.B., Camfield D.A., Hughes M.E., Woods W., CK K.S., White D.J., et al., A randomized controlled trial investigating the neurocognitive effects of Lacprodan(R) PL-20, a phospholipid-rich milk protein concentrate, in elderly participants with age-associated memory impairment: the Phospholipid Intervention for Cognitive Ageing Reversal (PLICAR): study protocol for a randomized controlled trial, Trials, 2013, 14, 404

[18] Pase M.P., Grima N., Cockere P., Stough C., Scholey A., Sali A., et al., The effects of long-chain omega-3 fish oils and multivitamins on cognitive and cardiovascular function: a randomized, controlled clinical trial, J Am Coll Nutr, 2015, 34, 21-31

[19] Tilden D.T., Kennedy D.O., Perry E.K., Ballard C.G., Wesnes K.A., Scholey A.B., Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers, Physiol Behav, 2005, 83, 699-709

[20] Wesnes K.A., McNamara C., Annas P., Norms for healthy adults aged 18-87 years for the Cognitive Drug Research System: An automated
set of tests of attention, information processing and memory for use in clinical trials, J Psychopharmacol, 2016, 30, 263-272
[29] Perry N.S., Houghton P.J., Sampson J., Theobald A.E., Hart S., Lis-Balchin M., et al., In-vitro activity of S. lavandulaefolia (Spanish sage) relevant to treatment of Alzheimer’s disease, J Pharm Pharmacol, 2001, 53, 1347-1356
[30] Ossoukhova A., Oven L., Savage K., Meyer M., Ibarra A., Roller M., et al., Improved working memory performance following administration of a single dose of American ginseng (Panax quinquefolius L.) to healthy middle-age adults, Hum Psychopharmacol, 2015, 30, 108-122
[31] Talb M.N., Shariff Z.M., Wesnes K.A., Saad H.A., Sariman S., The effect of high lactose-isomaltulose on cognitive performance of young children. A double blind cross-over design study, Appetite, 2012, 58, 81-87
[32] Pengelly A., Snow J., Mills S.Y., Scholey A., Short-term study on the effects of rosemary on cognitive function in an elderly population, J Med Food, 2012, 15, 10-17
[33] Kennedy D.O., Haskell-CF., Robertson B., Reay J., Brewster-Maund C., Luedemann J., et al., Improved cognitive performance and mental fatigue following a multi-vitamin and mineral supplement with added guarana (Paulinia cupana), Appetite, 2008, 50, 506-513
[34] Kennedy D.O., Stevenson E.J., Jackson P.A., Dunn S., Wishart K., Bieri G., et al., Multivitamins and minerals modulate whole-body energy metabolism and cerebral blood-flow during cognitive task performance: a double-blind, randomised, placebo-controlled trial, Nutr Metab (Lond), 2016, 13, 11
[35] Kennedy D.O., Veasey R., Watson A., Dodd F., Jones E., Maggini S., et al., Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males, Psychopharmacology (Berl), 2010, 114, 55-68
[36] Wightman E.L., Haskell-Ramsay C.F., Reay J.L., Williamson G., Dew T., Zhang W., et al., The effects of chronic trans-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow in healthy, young humans, Br J Nutr, 2015, 114, 1427-1437
[37] Wightman E.L., Haskell-Ramsay C.F., Thompson K.G., Blackwell J.R., Winyard P.G., Forster J., et al., Dietary nitrate modulates cerebral blood flow parameters and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation, Physiol Behav, 2015, 149, 149-158
[38] Steiner G.Z., Yeung A., Liu J.X., Camfield D.A., Blasio F.M., Pipingas A., et al., The effect of Salviae lotung (SLT) on neurocognitive and cardiovascular function in healthy adults: a randomised, double-blind, placebo controlled crossover pilot trial, BMC Complement Altern Med, 2016, 16, 15
[39] Stough C.K., Pase M.P., Cropley V., Myers S., Nolidin K., King R., et al., A randomized controlled trial investigating the effect of Pycnogenol and Bacopa CDR08 herbal medicines on cognitive, cardiovascular, and biochemical functioning in cognitively healthy elderly people: the Australian Research Council Longevity Intervention (ARCLI) study protocol (ANZCTR12611000487910), Nutr J, 2012, 11, 11
[40] Galasko D.R., Peskind E., Clark C.M., Quinn J.F., Ringman J.M., Jicha G.A., et al., Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures, Arch Neurol, 2012, 69, 836-841
[41] Ng T., Mazzarello S., Wang Z., Hutton B., Dranitsaris G., Vandermeer L., et al., Choice of study endpoint significantly impacts the results of breast cancer trials evaluating chemotherapy-induced nausea and vomiting, Breast Cancer Res Treat, 2016, 155, 337-344
[42] Betteridge D.J., DeFranzo R.A., Chilton R.J., PROactive: time for a critical appraisal, Eur Heart J, 2008, 29, 969-983
[43] Salaffi F., Franchignoni F., Giardino A., Ciappetti A., Gasparini S., Ottonello M., et al., Classical test theory and Rasch analysis validation of the Recent-Onset Arthritis Disability questionnaire in rheumatoid arthritis patients, Clin Rheumatol, 2013, 32, 211-217
[44] Heaney R.P., Nutrients, endpoints, and the problem of proof, J Nutr, 2008, 138, 1591-1595
[45] Devore E.E., Grodstein F., van Rood J.F., Hofman A., Stampfer M.J., Witteman J.C., et al., Dietary antioxidants and long-term risk of dementia, Arch Neurol, 2010, 67, 819-825
[46] Mangialasche F., Xu W., Kivipelto M., Costanzi E., Ercolani S., Pigliautile M., et al., Tocopherols and tocotrienols plasma levels are associated with cognitive impairment, Neurobiol Aging, 2012, 33, 2282-2290
[47] Isaacs E., Oates J.a.i.s.b.l I.E., Nutrition and cognition: assessing cognitive abilities in children and young people, Eur J Nutr, 2008, 47 Suppl 3, 4-24
[48] Sarris J., Logan A.C., Akbaraly T.N., Amminger G.P., Balanza-Martinez V., Freeman M.P., et al., Nutritional medicine as mainstream in psychiatry, Lancet Psychiatry, 2015, 2, 271-274
[49] Monteiro S., Ferreira F.M., Pinto V., Roque S., Morais M., de Sa-Calcada D., et al., Absence of IFNgamma promotes hippocampal plasticity and enhances cognitive performance, Transl Psychiatry, 2016, 6, e707
[50] Ong Lai Teik D., Lee X.S., Lim C.J., Low C.M., Muslima M., Aquili L., Ginseng and Ginkgo Biloba Effects on Cognition as Modulated by Cardiovascular Reactivity: A Randomised Trial, PLoS One, 2016, 11, e0150447
[51] Pincus T., Sokka T., Laboratory tests to assess patients with rheumatoid arthritis: advantages and limitations, Rheum Dis Clin North Am, 2009, 35, 731-734, vi-vii
[52] Lewis J.E., Melillo A.B., Tiozzo E., Chen L., Leonard S., Howell M., et al., A double-blind, randomized clinical trial of dietary supplementation on cognitive and immune functioning in healthy older adults, BMC Complement Altern Med, 2014, 14, 43
[53] Jackson P.A., Reay J.L., Scholey A.B., Kennedy D.O., Docosahexaenoic acid-rich fish oil modulates the cerebral hemodynamic response to cognitive tasks in healthy young adults, Biol Psychol, 2012, 89, 183-190
[54] Belcaro G., Luzzi R., Dugall M., Ippolito E., Pycnogenol(R) improves cognitive function, attention, mental performance and specific professional skills in healthy professionals aged 35-55, J Neuropsychiatry Sci, 2014, 58, 239-248
[55] Choudhary D., Bhattacharyya S., Joshi K., Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha
[56] Zamroziewicz M.K., Barbey A.K., Nutritional Cognitive Neuroscience: Innovations for Healthy Brain Aging, Front Neurosci, 2016, 10, 240
[57] Konagai C., Yanagimoto K., Hayamizu K., Han L., Tsuji T., Koga Y., Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized controlled trial in healthy elderly volunteers, Clin Interv Aging, 2013, 8, 1247-1257
[58] Boespflug E.L., McNamara R.K., Eliassen J.C., Schidler M.D., Krikorian R., Fish Oil Supplementation Increases Event-Related Posterior Cingulate Activation in Older Adults with Subjective Memory Impairment, J Nutr Health Aging, 2016, 20, 161-169
[59] Ackerman P.L., Cianciolo A.T., Cognitive, perceptual-speed, and psychomotor determinants of individual differences during skill acquisition, J Exp Psychol Appl, 2000, 6, 259-290
[60] Goff M.A., Personality-Intelligence Relations: Assessment of Typical Intellectual Engagement, Journal of Educational Psychology, 1992, 84, 537-552,
[61] Versace A.S.V., and Philips M., Predicting Behavioral and Emotional Dysregulation Trajectories in Symptomatic Youth from Structural Neuroimaging: A Machine Learning Approach., Neuropsychopharmacology, 2015, 40, S443-S611
[62] Akshoomoff N., Beaumont J.L., Bauer P.J., Dikmen S.S., Gershon R.C., Mungas D., et al., VIII. NIH Toolbox Cognition Battery (CB): composite scores of crystallized, fluid, and overall cognition, Monogr Soc Res Child Dev, 2013, 78, 119-132
[63] Langbaum J.B., Hendrix S.B., Ayutyanont N., Chen K., Fleisher A.S., Shah R.C., et al., An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer’s disease, Alzheimers Dement, 2014, 10, 666-674
[64] Hessl D., Sansone S.M., Berry-Kravis E., Riley K., Widaman K.F., Abeduto L., et al., The NIH Toolbox Cognitive Battery for intellectual disabilities: three preliminary studies and future directions, J Neurodev Disord, 2016, 8, 35
[65] Evans M, Roberts M, and Guthrie N, “Moving Science to Claims: A New Paradigm for Study Designs,” 2017.
[66] M. Evans, M. Roberts, and N. Guthrie, “Searching for Evidence to Move Science to Claims: A New Paradigm for Study Design,” 2017.
[67] M. Evans, Antony J.M, M. Undershultz, and N. Guthrie, “From Trials to Trials: The Augmented RCT for the Dietary Supplement Industry,” 2017.