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BACHELOR'S THESIS (TFG)

INTERACTION BETWEEN COGNITION AND NUTRITION

COGNITIVE ENHANCERS IN ORDER TO IMPROVE ATHLETES' PERFORMANCE

A LITERATURE REVIEW

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INTERACCIÓN ENTRE COGNICIÓN Y ALIMENTACIÓN.

POTENCIADORES COGNITIVOS PARA MEJORAR EL RENDIMIENTO DE LOS ATLETAS

(INTERACTION BETWEEN COGNITION AND NUTRITION.

COGNITIVE ENHANCERS IN ORDER TO IMPROVE ATHLETES' PERFORMANCE)

RESUMEN (*ABSTRACT*)

El uso de potenciadores cognitivos y suplementos está a la orden del día, especialmente entre los atletas pero… ¿Son realmente efectivos?

Para definir qué efectos beneficiosos se pueden esperar de un potenciador cognitivo, se exploró un modelo tridimensional que confiere la *energía mental;* compuesto por factores cognitivos, así como una parte emocional y otra relacionada con la motivación.

En esta revisión bibliográfica se investigó la literatura científica sobre dieciocho compuestos considerados *nootrópicos*. Se planteó si existe suficiente evidencia para recomendarlos a los atletas para potenciar dicha energía mental y, como consecuencia, su rendimiento deportivo. Resultó que solamente demostraron tener suficiente respaldo científico siete de las sustancias estudiadas, entre las que se encuentran la cafeína y la glucosa. La información más relevante de cada nootrópico (fuentes de obtención del compuesto, efectos que se esperan de él, mecanismos de acción, dosis efectiva, y si está o no incluído en la *Lista de sustancias prohibidas* de la *WADA*) se detalló en una tabla-resumen.

Finalmente se trataron temas relacionados con la ética, la seguridad, la legalidad, y el lugar que deberían ocupar estos suplementos en la alimentación de los atletas.

Uno de los mayores retos fue la limitada cantidad y calidad de los estudios e información halladas, y la falta de consenso científico sobre estos temas. De este modo, alentamos a que siga adelante el estudio en este campo tan prometedor.

PALABRAS CLAVE *(KEYWORDS): mental energy, sports performance, cognitive enhancers, nootropics, caffeine*

TABLE OF CONTENTS

ABBREVIATIONS

ATP- Adenosine triphosphate

BCAA- Branched-chain amino acids

CAF- Caffeine

CB1R- Cannabinoid receptor type 1

CBD- Cannabidiol

CDP-CHOLINE- Cytidine 5'-diphosphocholine or citicoline

CNS- Central Nervous System

Cr- Creatine

DA- Dopamine

DHA- Docosahexaenoic acid

EI- Emotional Intelligence

EMA- European Medicines Agency's

EPA- Eicosapentaenoic acid

GABA- Gamma-Aminobutyric Acid

GUA- Guarana

HMPC- The Committee on Herbal Medicinal Products

HT1A- Serotonin 1A Receptor

NA/ NE - Noradrenaline/ Norepinephrine

NMDA- N-methyl-D-aspartate receptor

PCr- Phophocreatine

PUFA- Polyunsaturated fatty acids

RR- Rhodiola Rosea

TCr- Theacrine

Th1- T helper cells type 1

TRPV1- Transient Receptor Potential cation channel subfamily V member 1

TYR- Tyrosine

INTRODUCTION

Physical abilities of most athletes at advanced levels are more homogeneous than their mental abilities, then, «the distinguishing feature of successful athletes competing at high levels is often their exceptional mental skills», as stated Silva in 1984. Therefore, *mental energy* is key to athletes, as sports performance is dependent on psychological traits such as: *cognition* (involving *learning and memory, attention and focus, creativity,* and *intelligence*), *mood,* and *motivation*. These features conform the *mental energy model* which will be further explained in the section *Psychological Functions Involved In Sports Performance* and in ***Fig. 4***.

Nutrition has shown to play an important role in optimal *mental energy or mental performance* trough abundance of research. The current research is focused on the study of the *nootropics*, also called *cognitive enhancers* or *smart drugs*.[1–3] These are compounds that can increase mental functions trough variety of physiological mechanisms and metabolic pathways, mostly related to neurotransmitters.

Literature on cognition-enhancing dietary constituents in sports performance is relatively sparse, and there are few published reviews on this topic. *Caffeine* and *Glucose* have the greatest number of published reports supporting their ability to enhance acute motor skill and cognitive performance in athletes, while other compounds such as *P-Synephrine* have very poor scientific evidence supporting their role on the cognitive functions.

In this study, eighteen different compounds postulated as nootropics have been addressed through a *literature-review* of the currently available data, in order to discuss whether they have enough evidence for supporting its use to improve athletes' performance.

OBJECTIVES

The objective of this *mini-review* is to study the available research literature in order to determine whether dietary constituents have enough scientific support for the improvement of motor skill and/or cognitive performance in young healthy adults, especially athletes. In order to summarize the reviewed literature, among our goals are the elaboration of a table with currently available scientific data, and the indication of future research directions.

Our initial hypothesis for starting this mini review is that we presume that nootropics can help improving the development of cognitive abilities for reaching a higher performance in athletes. On grounds of the latter hypothesis, we can formulate a number of questions, such as: «What can be considered as a nootropic? » or «Which cognitive functions are expected to be improved by these compounds? ».

In consequence, further objectives of this review are: *(I)* establishing on which mental traits future research should focus, *(II)* defining what nootropics are and how they are classified, *(III)* exploring the mechanisms by which they act on neurological functions, *(IV)* clarifying in which legal framework they lie, and finally, *(V)* reviewing the short and long term safety aspects for these compounds.

METHODS

The blueprint or starting point to carry out this literature-review, has been a document from Susan J Hewlings *Cognitive Sports Nutrition. Supplement Smart* from 2017[4], consisting in a set of slides that we have used as a first script for this project.

In order to extend on the information that Hewlings provides, we added new conclusions and points of view, and reviewed all the references and bibliography from Hewlings's document. Moreover, in order to help clarifying points of discussion, and contributing with new and updated information, a search of *MEDLINE (PubMed)* and the *Cochrane Library* databases was conducted for papers published up to December 2019, using the search terms: *"(DRUG OF STUDY p ex: "caffeine", "cannabidiol", …)" and "cognitive" or "cognition enhance" and "athletes" or "sports performance".*

As the conclusions of the reviewed studies vary much depending on the examined population, and because most research is focused on an aging population, we have excluded

corresponding studies and reviews. We thus consider only those articles which used athletes or young healthy population as participants. All are listed in the *References* section, which is the last section of this document, where they are cited consecutively in the order in which they appear.

The body of this study has been split in two main parts: the first one refers to the research and definition of the different mental functions that are relevant for athletic performance (**Fig. 4**). The first part is prerequisite to the second one, where the *nootropics* take central stage with the purpose of defining them and reviewing the currently available scientific data about eighteen of such compounds.

At the end of the document, a table (**Table 1.**) has been created which summarizes the most relevant information about the compounds and their functions. Furthermore, in the last section of the document (before *References*), conclusions and discussion about future research directions in this field are presented.

OVERVIEW

PSYCHOLOGICAL FUNCTIONS INVOLVED IN SPORTS PERFORMANCE

Multiple food and beverage products are marketed for their potential to enhance mental energy. The increasing sales volume of energy drinks or supplements reflects the desire among a significant proportion of individuals to enhance their mental energy. In order to determine which supplements might be relevant, it is necessary to first define what cognitive functions or traits are expected to be improved with them.

When reading the available literature on mental performance, it can be noticed that there is little consensus on how the authors define its characteristics, as it is challenging to measure it in an objective way. What complicates things further is that the results may vary depending on the studied population. In this section, diverse publications from different authors have been reviewed in order to give an overview of the distinction and definition of the mental functions involved in sports performance.

DEFINING "MENTAL ENERGY"

Progress in understanding *mental energy* or *mental performance* has been hampered by the lack of a scientific consensus on its definition, and this results in mental-energy claims that are usually inaccurate, misleading, or scientifically indefensible.

In 2006, O'Connor and colleagues [5] developed a model for examining nutrition-related claims towards mental energy. After great scientific literature reviewing, and the proposal of various preliminary models and definitions, they finally declared that «the weight of the evidence showed that mental energy is comprised primarily of three dimensions: cognition, the mood of energy, and motivation» (**Fig. 1**) as well as «there is substantial evidence that mental energy can be influenced by a large number of variables, including health status, age, nutritional status, and sleep» .

Other authors have concluded that *mental energy* is a three-dimensional construct as well. To Gorby [6], it also consists of *mood* (transient feelings about the presence of fatigue or

energy), *motivation* (determination and enthusiasm), and *cognition* (sustained attention and vigilance). Chiracu [7] defined it in a similar way, declaring that «The regulation of human actions is the result of specific interactions between the three main psychological structures supported by the individual's personality: cognition, emotion, and volition».

An extended model of *mental energy* has been elaborated and presented in the *Conclusions* section. (**Fig. 4**).

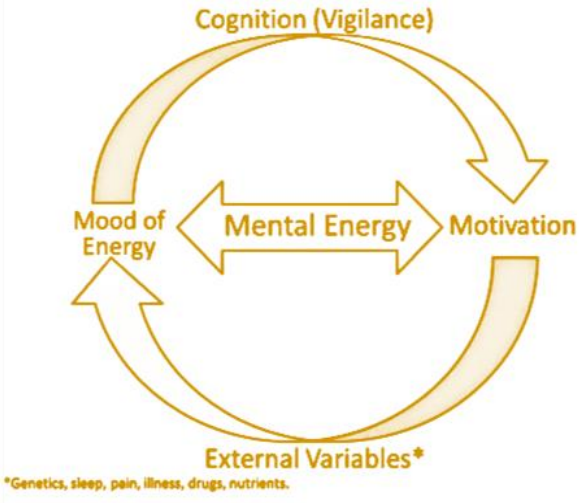

Fig. 1. Three-dimensional model of Mental energy. From: O'Connor PJ, Kennedy DO, Stahl S. *Mental energy: plausible neurological mechanisms and emerging research on the effects of natural dietary compounds.* 2019. [8]

THE NEUROLOGICAL MECHANISMS IMPLICATED IN MENTAL ENERGY

Recently O'Connor and co-authors [8] published an article related to the study of mental energy, where they go deeper in the definition of the mental-energy components. They show how they are related and hypothesize about the neurological processes involved. To them, the cognitive, motivational, and mood aspects of mental energy are related to different neurotransmitter systems and brain regions. This stands in contrast to other theories which postulated that the nootropics effects were mostly related to cerebral ATP.[9]

As far as cognition enhancement is concerned, *small molecule neurotransmitters* are the primary targets for nootropic intervention (**Fig. 2**), specifically, the following small molecule neurotransmitters[10]:

Acetylcholine, an excitatory neurotransmitter associated with neuromuscular junction activation, as well as with learning and memory formation, knowledge retention, and attention.

Serotonin, which plays an essential role in emotional regulation. Depending on the serotonin receptor site, serotonin activation may induce different outcomes. For example, prefrontal cortex receptors correlate with mental processing and perception, whereas hippocampal receptors are associated with learning and memory.

Dopamine, a catecholamine neurotransmitter that competes with serotonin, plays a key role in reward-seeking behaviour, and encompasses learning processes.

Noradrenaline, the primary acting neurotransmitter of the sympathetic nervous system, is involved in the physiological response to stress and panic as well as attention and focus processes.

Epinephrine (or *adrenaline*), a highly excitatory chemical that is commonly released as a response to physical stress, activates dormant sources of energy to be used by muscles, and has been shown to affect memory retention. [11]

Finally, ***Gamma-Aminobutyric Acid (GABA)***, is an inhibitory acting neurotransmitter that may contribute to enhance relaxation while ameliorating anxiety. Under stress conditions, GABA activity may also enhance immunity.

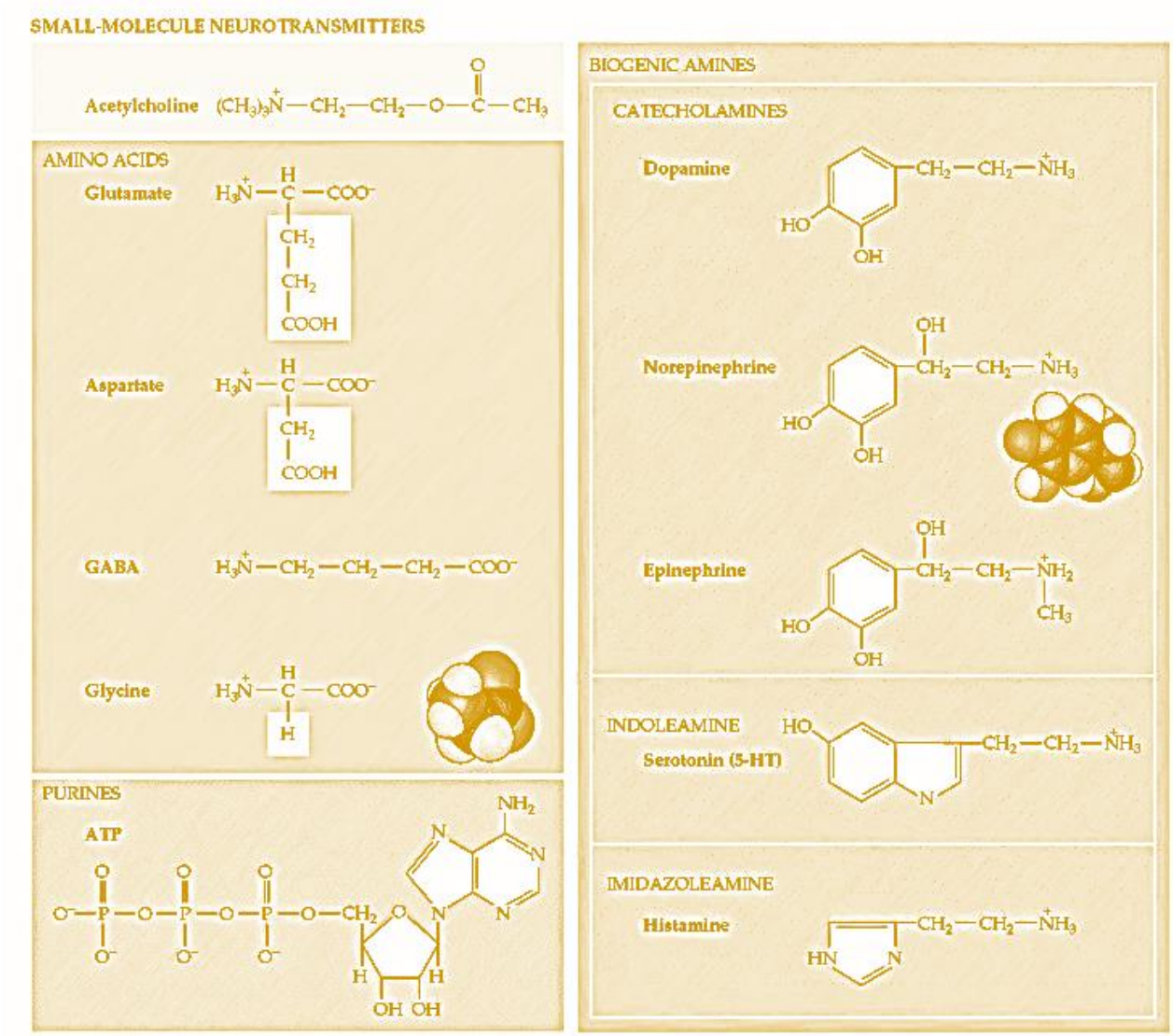

Fig. 2. Small molecule neurotransmitters. From: *Two Major Categories of Neurotransmitters.* Neuroscience. 2nd edition. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Sunderland (MA): Sinauer Associates; 2001.

The monoamine hypothesis of mood disorders[8] postulates that «dysregulation in norepinephrine, dopamine, and serotonin pathways causes the symptoms observed with these conditions». Even though these neurotransmitters have individually been associated with mental energy, the interconnections between them seem to be relevant as well. Serotonergic, dopaminergic, and noradrenergic innervations from the brainstem are associated with top-down control of the prefrontal cortex, and both noradrenergic and dopaminergic pathways have been identified between the prefrontal cortex and striatum.

On one hand, prefrontal cortex appears to be linked with executive processes affecting many diverse areas of cognitive function such as: short-term memory, information processing,

planning and reasoning, behavioural organization, attentional control and judgment.[12–14] On the other hand, the striatum seems to play a key role in motor output, performance, procedural memory, learning, acquisition of tasks and skills, and in drive, motivation, and re ward. [15] These psychological traits are part of the concepts which conform the *Mental energy model* (**Fig. 4**) that are explained below.

Cognition

Cognition is the most outstanding of the psychological structures that conform the mental energy concept. It has been defined as «*a suite of interrelated conscious (and unconscious) mental activities, including pre-attentional sensory gating, attention, learning and memory, problem solving, planning, reasoning and judgment, understanding, knowing and representing, creativity, intuition and insight, spontaneous thought, introspection, as well as mental time travel, self-awareness and metacognition (thinking and knowledge about cognition)*» by Mark J. Millan and 24 eminent researchers[16] that presented an exhaustive overview on cognitive dysfunction in psychiatric disorders published in Nature Reviews- Drug Discovery in the February 2012. To Lanni[17], the cognitive functions that contribute to mental performance can be divided in four distinct groups that are heavily interrelated (**Fig 3**)

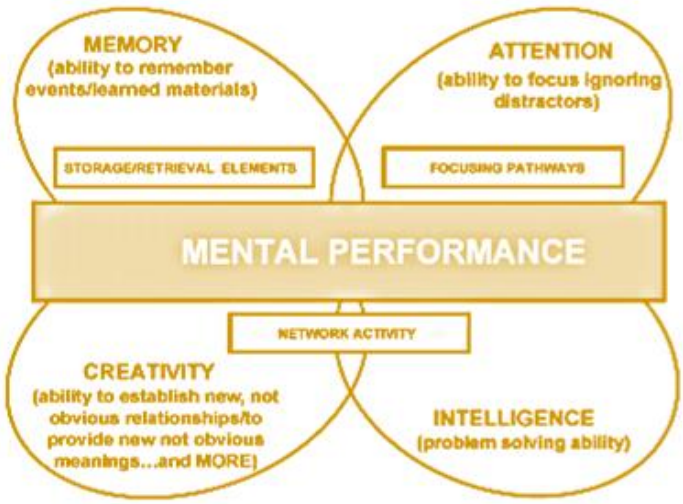

Fig 3: Cognitive functions contributing to mental performance. From: Lanni C, Lenzken SC, Pascale A, Del Vecchio I, Racchi M, Pistoia F, et al. *Cognition enhancers between treating and doping the mind.* Vol. 57, Pharmacological Research. 2008. p. 196–213. [17]

Sticking to this classification of the cognitive functions, we can summarize all of them into these four subgroups:

Learning and Memory: Memory involves storing and retrieval of information and consists in the working (short-term) and secondary (long-term) memory. Learning new information may involve serial acquisition of memories. Oftentimes, new memories are acquired on the basis of pre-existing knowledge, and thus an interaction between the new and existing memories is inevitable. In brief, memory is the ability to remember learned facts and materials. [18]

Attention: Attention is the ability to selectively process certain information while simultaneously inhibiting other information, the capacity of focusing on a task or thought while ignoring distractors. It is related to concentration, vigilance and reaction time, and involves alertness, orientation and psychomotor functions.

Alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli; orienting is the selection of information from sensory input; and executive control is defined as involving the mechanisms for resolving conflict among thoughts, feelings, and responses. Psychomotor functions range from highly automated gross motor activities like walking to highly skilled fine motor skills like knitting or precisely shooting a basketball through the defender's hoop.[19,20]

Creativity: Creativity is defined as the ability to generate ideas and problem solutions that are both novel and appropriate, or to establish new relationships that are not obvious between to mental items to provide new meanings. As to sport performance, creativity (divergent tactical thinking) is understood to be the surprising, original and flexible production of tactical and/or motor response patterns. [21]

Intelligence: Intelligence is the ability to acquire and apply knowledge and skills and involves the capacity of solving existing problems and the process of decision making. It is linked to the creativity processes to form the "network activity". [17]

Mood and emotion

Emotional Intelligence (EI) is defined as the ability to facilitate the recognition and regulation of emotions that, in turn, facilitate the generation of adaptive behaviour. In the context of sport performance, it has been found that EI relates to emotions, physiological stress responses, successful psychological skill usage, and more successful athletic performance [22] [23]. In a recent study, Skuys[24] found a negative relation between higher EI and the lack of

motivation in athletes. More specifically, it was concluded that «the self-reported abilities to perceive emotion and manage others' emotions were significantly related to intrinsic, integrated, and identified regulation, and only managing one's own emotions negatively related to athletes' poor motivation». The features that can be regulated effectively by drugs are the following:

Stress and anxiety management: Anxiety is defined as a negative emotional state consisting of a combination of feelings of nervousness, preoccupation, and apprehension related to the activation of the body, which includes a somatic component (physical anxiety) and a cognitive component (mental anxiety). At the athletic level, the phenomenon of state-anxiety appears immediately before and during competition. In contrast, trait-anxiety in the athletic world is characterized by a high degree of activation due to enduring successive negative experiences during competition. Thus, subjects displaying high levels of trait-anxiety perceive a broader range of situations as threatening and are more prone to suffer from state-anxiety more frequently and intensely. A proper management of the stress and anxiety in athletes seems to be key to their performance, and it can be approached via coaching processes or through a pharmacological treatment if necessary. [22]

Self-confidence: self-esteem is a construct comprised of cognitive and behavioural components, which are characterized by either emotional or physical aspects. The cognitive component relates to the general perception that each individual develops of themselves, and the emotional component refers to the process of self-assessment conducted by the individual. [22]

Motivation and volition

Motivation toward short- and long-term goals is of great importance concerning drive, determination, enthusiasm, volition and, consequently, performance in sports. Elite athletes consistently report higher motivation and commitment than non-elites [25], while poor motivation is related to worse performance [26]. According to sports psychology theories, motivation and drive depend on athletes' choice of goals and their persistence toward those. A distinction can be made between extrinsic motivation (toward, for example, monetary rewards) and intrinsic motivation for the pleasure an activity itself, and between primary (long

term) goals versus secondary, short term objectives. Motivation, as it has been already mentioned, is heavily related to the emotional intelligence and mental fatigue [27].

Mental fatigue interacts with performance by decreasing athletes' drive to exercise. From a psychological point of view, mental fatigue has two separate components: it can affect drive by increasing the perceived effort necessary for a given task, or by decreasing the perceived value of the reward that can be obtained[27]. It is associated with a broad range of 'side-effects' such as lack of energy, increased fatigability and feelings of lassitude, decreased feelings of motivation and alertness and changes in perception and mood [28]. Furthermore, research has shown that, as the level of fatigue increases, so does the risk of injuries, while the global performance decreases. [29]

NOOTROPICS

Cognitive enhancers or *nootropic drugs* (from the Greek root *noos* for mind and *tropein* for toward) are a heterogeneous group of compounds of diverse chemical composition and biological roles that increase mental functions including memory, motivation, creativity, concentration, and attention.[17] The term nootropics was coined in 1972 when memory enhancing properties of *piracetam*- one of the first and most known drug recognized as a cognitive enhancer- were observed in clinical trials. In the meantime, hundreds of drugs have been evaluated in clinical trials or in preclinical experiments. [2,30]

CLASSIFICATION

To classify the compounds, Froestl et al.[2,31,32] propose a concept to assign cognition enhancing drugs to 19 categories* according to their mechanism(s) of action. For drugs, whose mechanism of action is not known, they are either classified according to their structure or their origin.

***CATEGORIES**

1. Drugs interacting with Receptors
2. Drugs interacting with Enzymes
3. Drugs interacting with Cytokines
4. Drugs interacting with Gene Expression
5. Drugs interacting with Heat Shock Proteins
6. Drugs interacting with Hormones
7. Drugs interacting with Ion Channels
8. Drugs interacting with Nerve Growth Factors
9. Drugs interacting with Re-uptake Transporters
10. Drugs interacting with Transcription Factors
11. Antioxidants
12. Metal Chelators
13. Natural Products
14. Nootropics ("Drugs without mechanism")
15. Peptides
16. Drugs preventing amyloid- aggregation
17. Drugs interacting with tau
18. Stem Cells
19. Miscellaneous

EVIDENCE ON NOOTROPICS

B GROUP VITAMINS

In particular, B vitamins intake has been thought to reduce the risk of later adulthood cognitive dysfunction. Multiple mechanisms linking B vitamins to cognitive function have been observed, mainly through their influence on homocysteine metabolism. [33] Inadequate intake of B vitamins also seems to potentially have a negative effect on mental energy due to their role in overall energy production, as precursors of key co-factors in the citric acid cycle, as well as their role in brain function and neurotransmitter synthesis.

However, the current evidence available showed no association for cognitive benefits of vitamins B6 or B12 as a mono-therapy, and recent systematic reviews provide no clear evidence that supplementation with vitamin B6, B12 and/or folic acid improves dementia outcomes or slows cognitive decline, even though it may normalize homocysteine levels. [34,35]

Supplements based on vitamin B group compounds cannot be definitively recommended to athletes because there are no generally valid reference values [36] or enough quality evidence to support its use. [8]

BRANCHED-CHAIN AMINO ACIDS

Branched-chain amino acids (BCAAs) *(leucine, isoleucine, and valine)* are large, nonpolar, neutral amino acids- because of their side chains. They have been suggested as a potential nutritional restorative agent to central fatigue during prolonged exercise, possibly mediated by their proposed impact on serotonin synthesis in the brain. The effects of branched-chain amino acid intake on cognitive performance during exercise have been tested in only a few studies. Some of them expose BCAA supplementation, which seems to modify only slightly the exercise-induced changes in mood and in cognitive performance, respectively. These results are more consistent when the level fatigue is more pronounced. [3,37,38]

However, evidence shows that BCAA supplementation before and after exercise has beneficial effects for decreasing exercise-induced muscle damage and promoting muscle-protein synthesis. Recent works indicate that BCAA supplementation recovers peripheral blood mononuclear cell proliferation in response to mitogens after intense exercise, as well as plasma glutamine concentration. The BCAA also modifies the pattern of exercise-related

cytokine production, leading to a diversion of the lymphocyte immune response towards a Th1 type. [39]

Despite the potential mechanism behind the hypothesis that branched-chain amino acid intake would benefit athletes, the available experimental evidence in athletes is sparse and controversial, so there is not enough evidence supporting them to be recommended to enhance motor skills or cognition for sports performance. Otherwise, it is possible to consider the BCAA as a useful supplement for muscle recovery and immune regulation for sports events. [3,37,39]

CAFFEINE

Caffeine is, by far, the drug that has the greatest number of publications supporting its cognitive enhancing function. In 2019, the search in the scientific database *Pubmed*, returned a total of 1605 results for these search terms: «*caffeine* and «*cognitive*» or «*sports performance*» or «*athletes cognitive*»».

Caffeine (CAF) is among the most frequently used psychoactive substances in the world. Lack of mental energy is one of the leading reasons adults turn to dietary supplements, mainly hoping to improve their energy level, and most of them consume caffeine-containing products for the same reason. CAF can be ingested from natural sources such as coffee and chocolate beans, tea leaves, kola nuts, and others, or can be artificially synthesized and included in food and drinks. [40]

The potential effects of caffeine, at the cellular level, can be explained by three mechanisms of action: as an antagonist to adenosine receptors, especially in the central nervous system; the mobilization of intracellular calcium storage; the inhibition of phosphodiesterases. [41]

Typically, the ergogenic effects of CAF have been observed with doses ranging from 3–9 mg/kg/body mass (BM). However, some individuals may be liable to CAF's anxiogenic effects, whilst others are susceptible to its ability to induce sleep disturbances and insomnia. [42]

A systematic-review in 2017, where 17 intervention studies across sport, exercise, and cognitive performance were analysed exploring CAF expectancies, concluded that CAF improves numerous cognitive and behavioural mechanisms that are associated with successful sport, exercise and cognitive performance, including: alertness, concentration,

energy levels, and self-reported feelings of fatigue. CAF has also been observed to improve sport, exercise and cognitive performance directly. [41,42]

In other studies -that where not part of the mentioned review- which compared the effects of CAF intake concluded that: participants were significantly faster after CAF ingestion when compared with carbohydrates only or placebo, showing that CAF can significantly improve endurance performance and complex cognitive ability during and after exercise and that these effects may be salient for sports performance in which concentration plays a major role [43] ; there was an enhanced speed of information processing after exercise, interesting as decision-making processes are crucial in the performance of many sports[44]; and CAF facilitates performance in tasks involving working memory to a limited extent but then seems to hinder performance in tasks that heavily depend on working memory. Furthermore, CAF appears to rather improve memory performance under suboptimal alertness conditions[45]; most studies, nevertheless, found improvements in reaction time.

CANNABIDIOL (CBD)

Cannabidiol (CBD), an acid metabolite THC-COOH, is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of *Δ9-tetrahydrocannabinol* (THC). Preclinical and clinical studies show CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions- including antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties. In recent years, CBD has attracted increasing interest as a potential anxiolytic treatment.

CBD neuroprotection is due to its antioxidant and anti-inflammatory activities and the modulation of a large number of brain biological targets (channel receptors) involved in the development and maintenance of neurodegenerative diseases.[46]

Cannabidiol can reduce fear expression acutely by disrupting fear memory reconsolidation and enhancing fear extinction, both of which can result in a lasting reduction of learned fear.[47]

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviours. Specifically, the *cannabinoid type 1 receptor* (CB1R activation is essential to negative feedback of the neuroendocrine stress response, and

protects against the adverse effects of chronic stress), the *serotonin 5-HT1A receptor* (an established anxiolytic target), and the *transient receptor potential vanilloid type 1 receptor* (TRPV1). In addition, CBD may also regulate, directly or indirectly, the *peroxisome proliferator-activated receptor-γ*, the *orphan G-protein-coupled receptor 55*, the *equilibrative nucleoside transporter*, the *adenosine transporter*, additional *TRP channels*, and *glycine receptors*. [48]

A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities. Acute systemic administration of CBD produces a typical 'bell-shaped' dose–response curve, being anxiolytic at low and intermediate doses but not at high doses. [47,48]

CITICOLINE (CDP-CHOLINE)

CDP-choline (cytidine 5'-diphosphocholine) is a phospholypid precursor essential for the synthesis of *phosphatidylcholine*, one of the cell membrane components. CDP-choline is the endogenous compound normally produced by the organism. When the same substance is introduced as a drug it can be called *citicoline*.

Numerous preclinical data support the view that it displays neuroprotective properties by supporting biosynthesis of cellular phospholipids. [49]

Furthermore, there is some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short to medium term. The number of studies supporting this is however minimal. Research findings support that CDP-choline cognitive enhancement involves multiple mechanisms including facilitated nicotinic cholinergic action. [50,51]

The lack of acute and chronic toxicity of citicoline has been repeatedly confirmed as the compound is quickly catabolized and the products arising are subsequently available for diverse biosynthetic pathways and ultimately excreted as carbon dioxide. [49]

Further research is required to support the indication of citicoline to improve the cognitive performance of the athletes.

CREATINE

Creatine is a naturally occurring compound that is synthesized from the amino acids arginine, glycine and methionine through a two-step reaction, it is found primarily in meat products and is produced endogenously by the liver, kidneys, and pancreas. [52]

In general, creatine is implicated in cellular energy homeostasis being its main function to immediately supply energy to tissues with increased energy demands, such as muscle and brain. Brain cells use the phosphorylated adenine nucleotide ATP for energy production (Erecińska and Silver, 1989). The phosphate creatine/creatine (PCr/Cr) system is linked to adenine nucleotides through the creatine phosphokinase reaction. [53]

Creatine supplementation has been proven safe and is usually used by athletes to increase their athletic performance. In addition, creatine is an essential compound for the brain and may aid various brain regions in terms of energy supply and neuroprotection. There is also evidence that creatine contributes to neuroprotection by reversing mitochondrial dysfunction in neurodegenerative diseases. [52,53]

A systematic review in 2008 [53] examined the effects of oral creatine administration on cognitive function in healthy individuals. The studies included in this review provide evidence that oral creatine intake may improve performance on short term memory and intelligence and reasoning tasks. For other aspects of cognition, such as attention, executive function, response inhibition, word fluency, reaction time and mental fatigue, the results were inconclusive.

CURCUMIN

Curcumin is a constituent of the spice turmeric, and supplements are often ingested for anti-inflammatory effects, being used to decrease muscle damage at a dose of about 5 g/day. [54]

In animal models, curcumin has been shown to not only reduce systemic inflammatory markers but also to improve cognitive function, increasing memory acquisition ability and enhancing nonspatial memory in aged mice and rats. However, direct link between improvements in inflammatory status and cognitive benefits due to curcumin still needs to be established. [55]

In humans, despite epidemiologic studies also suggest a link between curcumin consumption and cognitive benefits, recent studies suggest that curcumin supplementation does not significantly improve motor and cognitive functions in healthy adults. It is possible that curcumin may enhance these functions in groups with greater baseline impairments, including adults greater than 75 years of age and/or patients with clinical disorders. [54,56]

GINKGO BILOBA

The herbal product *Ginkgo biloba* is taken frequently with the intention of improving cognition in healthy population or preventing or delaying cognitive impairment associated with aging and neurodegenerative disorders. It has been suggested to increase cerebral blood flow, reduce blood viscosity, eradicate free radicals, and modify neurotransmitter systems. However, evidence from adequately powered clinical trials is lacking regarding its effect on long-term cognitive functioning or athletes' performance. [3,57]

Due to inconsistent findings and methodological quality of reviewed trials, more research is warranted to confirm the effectiveness and safety of ginkgo biloba, especially with the purpose of enhancing cognitive functions in athletes.

GINSENG

Ginseng is a plant belonging to the genus Panax. Its roots, stems and leaves have been used in traditional herbal medicine. Ginseng and its active components have exhibited a wide range of characteristics, including antioxidant, anti-aging, anti-fatigue, anti-inflammatory, and immunomodulatory. In addition, in models of neurological disorders, the active components of ginseng showed anti-depressive and anti-stress activities. Ginseng constituents exert their effects by modulating cholinergic, glutaminergic, and other molecular signaling pathways that are vital for cognitive activity. [3,58,59]

Recent studies collected in a systematic-review from 2018 have reported on the potential therapeutic efficacy of active ginseng components, but more studies utilizing novel techniques are needed to confirm its utility in the context of sports performance. [59]

GLUCOSE

Glucose is the primary monosaccharide in metabolism and most abundant dietary sugar source, for ~80% of the end product of CHO digestion, as complex sugars and carbohydrates get broken down into glucose. It is one of the prime sources of *fuel* serving the *central nervous system* (CNS). The brain requires a continual supply of glucose, an estimated 120g per day. Thus, changes in glucose availability impact on normal brain functioning and associated cognitive processes. It has been proposed that glucose boosts cognitive performance through direct action on the brain by modifying neural metabolism, neural activity, or by influencing the synthesis of neurotransmitters. [60]

Although the majority of studies have administered an acute 25-50 g glucose dose, the data from a study of the response and glucose regulation on cognition suggested that despite an acute rise in blood glucose levels has some short-term improvements of cognitive function, a more stable blood glucose profile, which avoids greater peaks and troughs in circulating glucose is associated with better cognitive function and a lower risk of cognitive impairments in the longer term. Therefore, a habitual diet that secures optimal glucose delivery to the brain in the fed and fasting states should be most advantageous for the maintenance of cognitive function. [61]

A systematic-review from 2018 suggests a specific enhancing effect of glucose intake on hippocampal-dependent cognitive functions: recognition memory; visuospatial memory and visuospatial functioning. Furthermore, glucose enhancement of cognitive domains that are not closely associated with hippocampal function has also been demonstrated such as processing speed and reaction time, working memory; problem solving, and attention have all been shown to be sensitive to an acute glucose load. A number of studies examining the effects of glucose on cognitive performance additionally measured participants' subjective ratings of alertness, energy, and fatigue. The facilitative effect of glucose on sustained attention and vigilance has been demonstrated, but not consistently. [3,62,63]

However, there is little evidence to support the facilitative effects of glucose intake on the mood and motivation dimensions of mental energy. We were unable to find any study that has specifically measured improvement in these traits after glucose intake. Therefore, the evidence to date does not support the specific subjective mood enhancing effects of glucose

intake, and further research is required to warrant the effectiveness on cognitive enhancement. [64,65]

On the other side of the ledger, carbohydrate ingestion at a rate of ≥1.2 g carbohydrate per kg body mass per hour appears to maximise post-exercise muscle glycogen repletion rates, being recommended to ensure an optimal recovery after, high intensity exercise sessions and to satisfy the brain and body demands prior to them. [66]

GUARANA

The seeds of the *Guarana* plant (GUA) *Paullinia cupana* are known as a stimulant, aphrodisiac, and astringent. Its composition includes caffeine, theobromine, and theophylline; and it is valued mainly for its stimulant property because of its high content of caffeine, which can be up to 6% in the seeds. Approximately 70% of the production is used by the industry of soft and energy drinks. The other 30% becomes guarana powder for direct consumption in capsules or dilution in water, or it serves as a raw material for the pharmaceutical and cosmetics industries. [3,67]

A placebo-controlled, double-blind, randomized, balanced cross-over study demonstrated that the administration of a vitamin and mineral complex with GUA attenuates mental fatigue and improve performance during cognitively demanding tasks. [68]

Another study showed that there is an interaction between GUA and an enhancement in the speed of information processing after exercise. This finding is particularly interesting as decision-making processes are crucial in the performance of many types of sports. [44]

The active ingredient in guarana is thought to be caffeine. However, some have postulated that the positive effects of guarana on cognitive performance are not likely attributable to caffeine because the caffeine content of guarana is low (as little as 9 mg of caffeine or less) at the doses of guarana found to be effective (75 mg). Otherwise, in our previous research on CAF, we found that it compound was effective at dosages of 3-9 mg/kg (BM). [3]

Overall, guarana is generally recognized as safe as a dietary ingredient marketed for its flavour and caffeine content. If guidelines for caffeine intake are respected, guarana consumption is not likely to be associated with any serious health risks. [67]

Although the consumption of guarana - usually in energy drinks - is popular, there is very little evidence to support its use to improve cognitive functions in healthy athletes, beyond its effects derived from caffeine.

L-CARNITINE

L-carnitine has been suggested as a possible cognitive enhancer. L-carnitine has been used as an ergogenic aid for professional athletes and as a dietary supplement in the physically active population. It is sold on its own as a dietary supplement or in some mixed supplements or *energy drinks*. However, it is also found naturally in the diet - especially in meat- and can be produced in the body.

Due to the limited number of included trials, short-term treatment, and inadequate reporting, it is difficult to draw any conclusions about the efficacy or safety of L-carnitine for cognitive enhancement in healthy adults. Well-designed, randomized, placebo-controlled trials of L-carnitine for cognition enhancement in cognitively healthy people, with large samples and relatively long-term follow-up, are still needed. [69]

Otherwise, there is evidence for a beneficial effect of L-carnitine supplementation on reducing physical and mental fatigue, recovery and delay of exhaustion after exercise. Specifically it has shown to play a decisive role in the prevention of cellular damage and to favourably affect recovery from exercise stress. [70–72]

L-THEANINE

L-theanine (N-ethyl-L-glutamine) is a major amino acid found in green tea that has been historically reported as a relaxing agent, with evidence suggesting it increases brain serotonin, dopamine, GABA levels and has micromolar affinities for *AMPA, Kainate and NMDA receptors*. In addition, has been shown to exert neuroprotective effects in animal models possibly through its antagonistic effects on *group 1 metabotrophic glutamate receptors*. Behavioural studies in animals suggest improvement in learning and memory. [73,74]

The main focus of the study of L-theanine is in its effects, when in combination with caffeine, on cognition and mood in healthy volunteers – as there is lack of convincing evidence to show L- enhances cognition.[3]

In a meta-analysis from 2014, tea constituents L-theanine and caffeine in combination were found to induce increases in alertness and attention switching accuracy. Small enhancement of unisensory visual and auditory attention accuracy was also found following L-theanine and caffeine consumption. [3,75]

The combination of around 100 mg of L-theanine with 50 mg of caffeine has shown to be effective to focus attention during a demanding cognitive task. [76]

The results of acute and chronic toxicity tests conducted on the safety of theanine express that L-theanine is reliable in general even if it is consumed too much with diet. [77]

N-3 POLYUNSATURATED FATTY ACIDS

The *n-3 PUFA* are a group of polyunsaturated fatty acids characterized biochemically by a double bond at the third carbon from the methyl end of the carbon chain. These essential nutrients have to be introduced through diet. They can be found in fish such as sardines, salmon, tuna, halibut, and other seafood such as algae and krill, and in lake trout, in some plants, and nut oils. These PUFAs, which are stored in cellular membrane phospholipids, are responsible for numerous cellular functions including the maintenance of the cell membrane structure, fluidity, signalling, and cell-to-cell interaction.[78,79]

Although the current clinical literature on *DHA (docosahexaenoic acid)* and *EPA (eicosapentaenoic acid)* for brain function is still relatively small compared to the literature on circulatory benefits, the weight of the current evidence supports the research of their utility for cognition, behaviour, and mood, as well as for early brain development and overall mental performance. [80]

The effects of n-3 PUFA on health are mainly derived from its anti-inflammatory proprieties and its influence on immune function. A big part of the studies has focused on increasing metabolic capacity, delaying the onset of fatigue, and improving muscle hypertrophy and neuromuscular function. DHA is proven essential to brain development, whereas EPA seems more influential on behaviour and mood. Both DHA and EPA generate neuroprotective metabolites. [81–83]

Furthermore, poor omega-3 fatty acid status has been linked to anxiety in the general population. In 2015, Patrick [84] proposed mechanisms by which EPA increases serotonin

release from presynaptic neurons by reducing E2 series prostaglandins, and DHA influences serotonin receptor action by increasing cell membrane fluidity in postsynaptic neurons.

To summarize, there is marginal evidence that n-3 PUFA supplementation affects cognition in subjects who are n-3 PUFA deficient. However, there is no major evidence of an effect in the general population, nor has it demonstrated that it can significantly alter cognitive performance in -cognitively- healthy people. This has important implications given the widespread advertisement and consumption of n-3 PUFA; claims of cognitive benefit should be limited until new evidence is available. [85,86]

P-SYNEPHRINE

P-synephrine is a protoalkaloid with sympathomimetic properties extracted from bitter oranges, used for weight loss and management, sports performance, appetite control, energy, and mental focus and cognition. [87]

The primary effects when ingested prior to exercise, appear to be to improve perceptions about drive to perform and cognitive function with limited to no effects on muscular endurance. However, the addition of 20 mg of *p*-synephrine to the pre-workout supplement used in Jung's study did not appear to provide additive benefit. Further research to examine the safety and efficacy is warranted. [88]

RHODIOLA ROSEA

Rhodiola rosea (RR) is a plant used in traditional medicine in Asia and Eastern Europe. It has been associated with stimulating the nervous system, reducing depression, enhancing physical performance, reducing fatigue levels, abating acute mountain sickness, having adaptogenic properties, and providing greater altitude training benefits in improving aerobic performance in long-distance runners.[89] RR is the main adaptogen approved by the **HMPC*** for the indication *stress*. [90]

A systematic review from 2015[90] concluded that «RR demonstrates

***The Committee on Herbal Medicinal Products (HMPC)** is the European Medicines Agency's (EMA) committee responsible for compiling and assessing scientific data on herbal substances, preparations and combinations, to support the harmonisation of the European market.*

multi-target effects on various levels of the regulation of cell response to stress, affecting various components of the neuroendocrine, neurotransmitter receptor and molecular networks associated with possible beneficial effects on mood». It possesses a unique mechanism of action: it normalises the release of stress hormones while simultaneously boosting energy metabolism via activation of ATP synthesis in mitochondria, and produces a variety of mediator interactions with molecular networks of neuroendocrine-immune and neurotransmitter receptor systems likely to be involved in the pathophysiology of depression. In contrast to conventional antidepressants, RR extract appears to be well-tolerated in short-term studies with a favourable safety profile. [91,92]

A wide variety of preclinical *in vivo* and *ex vivo* studies conducted in cell lines and animal models have elucidated the presence of several biochemical and pharmacological stress-reducing actions of RR. [90] However, findings indicating RR directly increases exercise performance are contradictory due to a variety of factors such as poor scientific controls or sample sizes.[93]

THEACRINE

Theacrine (1,3,7,9-tetramethyluric acid) is recently developed compound similar to caffeine that appears to operate similarly as an adenosine receptor antagonist. Theacrine is reported to possess diverse pharmacologic activity including antioxidant, anti-inflammatory, anti-depressive, and sedative properties. [94,95]

There is little research on this compound; one study that has investigated the effects of theacrine independently on subjective measures of mental well-being where energy, focus, and concentration increased after the drug administration but with no dose-response effect[96]; another study that tested the effects on muscular strength and endurance in resistance trained males, with few significant beneficial effects on strength training and endurance during bench and leg presses [95]; and a recent study whose results indicate that a combination of 150 mg Caf with 125 mg TCr produce some modest cognitive benefits- not seen with ingestion of 275 mg of TCr alone- supporting the possibility that there is a synergistic effect for these supplements, particularly given that the dose of each in combination was less than that given independently. [97]

It may hold some promise given the fact it has been shown to increase mood and subjective measures of cognitive function with no adverse side effects or habituation, in contrast to caffeine.

TYROSINE

The amino acid *tyrosine* (TYR) is the precursor to the catecholamine neurotransmitters *dopamine* (DA) and *norepinephrine* (NA). Increasing the TYR uptake may positively influence catecholamine-related psychological functioning. [98]

Oral doses of TYR increase circulating concentrations of NA, and DA both in the CNS and periphery. These are heavily involved in the regulation of body functions during physical stress and exercise.[99]

The potential of using TYR supplementation appears to prevent declines in various aspects of cognitive performance and mood. To treat clinical disorders seems limited and its benefits are likely determined by the presence and extent of impaired neurotransmitter function and synthesis. Likewise, the potential of TYR supplementation for enhancing physical exercise seems minimal as well, perhaps because the link between physical exercise and catecholamine function is mediated by many other factors. In contrast, TYR does seem to effectively enhance cognitive performance, particularly in short-term, stressful and/or cognitively demanding situations.[100,101]

Then, TYR is an effective enhancer of cognition in specific situations, during acutely stressful situations, central catecholamine neurons are unable to synthesize sufficient neurotransmitters; when neurotransmitter function is intact, and DA and/or NE is temporarily depleted.

CONCLUSION

The increasing *lifestyle* use -rather than medical reasons- of *smart drugs* and other supplements indicates the desire of healthy people to improve themselves, what is especially true for athletes. However, the scientific evidence that supports the use and prescription of these drugs in healthy population is sparse and is lacking consensus.

This mini-review has included only eighteen different nootropics -widely advertised by nootropics selling companies and used commonly by athletes, to improve their mental energy- out of the great number of both natural and synthetic compounds available in the industry and market.

The *Mental energy* model that has been proposed (**Fig. 4**), in order to clarify the traits that we are expecting to improve with these drugs, is a three-dimensional model composed by: *Cognition; Mood and Emotion;* and *Motivation and Volition*. Within the cognitive framework, the primary traits collected are: *Learning and Memory; Attention/Alertness; Creativity;* and *Intelligence*. The *Mood and Emotion* level comprises features such as: *Emotional Intelligence*; *Stress and anxiety management*; and *Self-confidence*. Finally, the motivational factor is composed by: *Motivation* itself; and *Mental fatigue*.

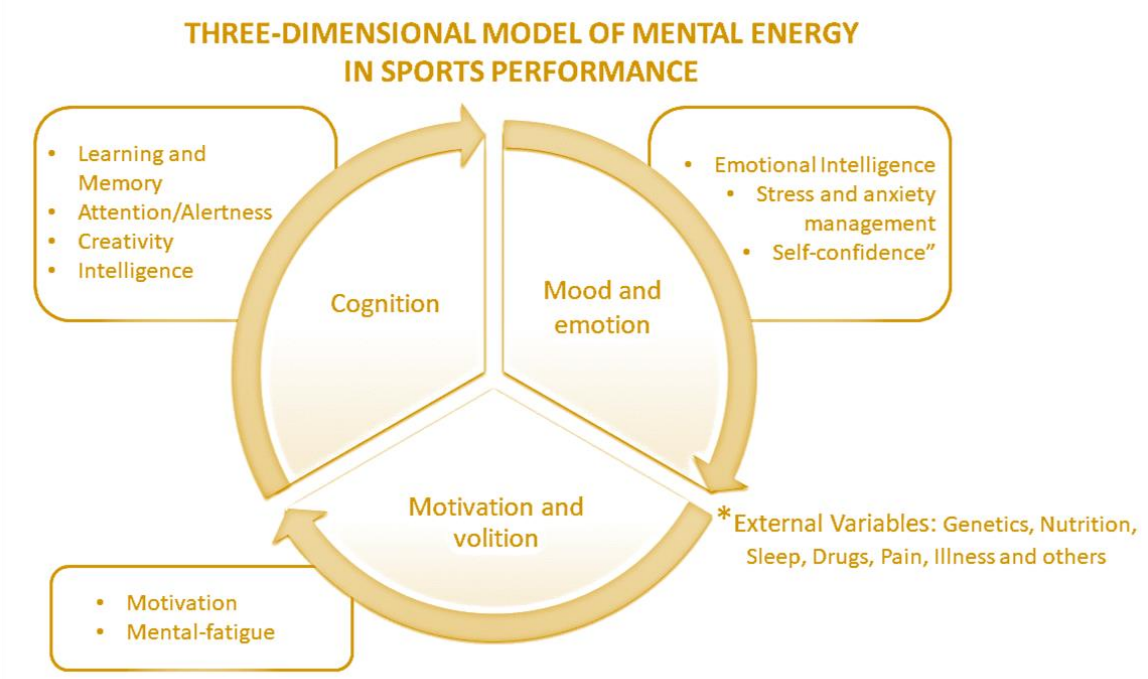

Fig. 4. ***Three-dimensional model of mental energy in sports performance***

The lack of scientific consensus in the definition and measurement of these traits, turns out to be a major obstacle for contrasting the literature within this area of knowledge. A standard assessment form would be of great interest in order to unify the conclusions derived from future studies related to mental energy in sports performance. We suggest the *Athletic Mental Energy Scale* (AMES), a recent model of assessment proposed in 2018 by Lu and other authors[102], which seems to be the first measure of mental energy in sports and psychology with sufficient reliability and validity. AMES creates a unique model of mental energy specific to the sport comprises 6 factors: *vigour, motivation, confidence, tireless, concentration,* and *calm*.

Aside from the mental performance enhancing functions that the nootropics may provide, they can also play a role in other aspects that are of interest for improving sports performance. We would like to consider, as compounds with these effects may provide further advantages and be more convenient.

Summarizing, our main interest was to study mental strength and non-mental strength aspects that play an important role in athletic performance, and which can be modified through the use of nootropics:

- *With respect to **mental performance**: (A)*
    - *Boost of the overall **cognitive functions**: learning, memory, creativity, intelligence (A1)*
    - ***Anxiety and stress** reduction before competitions or exercises (A2)*
    - *Improvement of **attention and concentration**, in order to increase the probability of success and decrease the risk of injury (A3)*
    - *Improvement of **mood** for achieving a higher **motivation** (A4)*
    - *Reduction of the **perception of fatigue**, as this one increases the likelihood of losing strength, concentration and motivation which leads to an increased risk of injury (A5)*
- *With respect to **non-mental performance**: (B)*
    - *Help for providing adequate **energy** to maintain muscle function, considering exercise speed (sprint over short distances) or long duration (marathon) (B1)*
    - *Ameliorate **recovery** after training or competition (B2)*

The following table (**Table 1**) summarizes the systematic survey carried out in our study. The eighteen (18) compounds that we reviewed have been the following: *B group Vitamins; Branched-chain amino acids (leucine, isoleucine, and valine); Caffeine; Cannabidiol; Citicoline (CDP-Choline); Creatine; Curcumin; Gingko Biloba; Ginseng; Glucose; Guarana; L-Carnitine; L-Theanine (+ Caffeine); n-3 Poliunsatured Fatty Acids; P-Synephrine; Rhodiola Rosea; Theacrine (+ Caffeine);* and *Tyrosine.* In the table, we included the data that was deemed to be relevant for the purpose of our study: the name of the drug or compound; sources from which it can be obtained; expected effects for cognitive and non-cognitive enhancement (following the alphanumeric legend indicated in the previous paragraph); the postulated mechanisms of action, the effective dose; safety aspects and side effects; the author's personal point of view about whether there is enough evidence supporting its use to improve mental energy in athletes - according to the literature reviewed-; and the current (2019) state within the *World Anti-Doping Agency* (WADA)'s framework*.

The compounds have been reviewed through "Global DRO" webpage- based on the current **WADA's "Prohibited List"- in December 2019, for "United Kingdom" as country, with "Athletes" for User type filter and "Basketball" for Sport filter.*

Table 1. ***Evidence on nootropics. Literature-review***

Compound	Sources	Expected effects	Postulated mechanism of effect	Effective dose	Safety / Side Effects	Evidence (*)	WADA 2019
B group Vitamins	Natural sources such as whole grains, meat, eggs, dairy products, legumes, seeds and nuts	A1;A5;B1	Influence on homocysteine metabolism; precursors of key cofactors in the citric acid cycle	NA	Well tolerated	N	Not prohibited
Branched-chain amino acids	Natural protein sources such as meat, milk, eggs, legumes, …	A5;B2	Possible impact on serotonin synthesis; decrease of exercise-induced muscle damage; promoting muscle-protein synthesis; cytokine production modifier	90 mg/kg	Well tolerated	N	Not prohibited
Caffeine	Natural sources (coffee, chocolate beans, tea leaves, kola nuts, etc.) or artificially synthesized (energy drinks or gels)	A1;A3;A5	Antagonism of adenosine receptors; mobilization of intracellular calcium storage; inhibition of phosphodiesterases	3–9 mg/kg/(BM)	Anxiogenic effects, sleep disturbances and insomnia	Y	Not prohibited
Cannabidiol	Phytocannabinoid constituent of Cannabis Sativa	A2	Interactions with several receptors (CB1R, HT1A, TRPV1, …)	1500 mg/day	Well tolerated	Y	Conditional
Citicoline (CDP-Choline)	Citicoline is the name of CDP-Choline (endogenous compound) when introduced as a drug.	A1	Facilitates nicotinic cholinergic action; supports biosynthesis of cellular phospholipids	NA	Well tolerated	N	NA

Compound	Sources	Expected effects	Postulated mechanism of effect	Effective dose	Safety / Side Effects	Evidence (*)	WADA 2019
Creatine	Naturally occurring compound synthesized from arginine, glycine and methionine	A1;B1	(PCr/Cr) system to supply energy to tissues, reversing mitochondrial dysfunction	20 g/ day for 5-7 days	Well tolerated, bloating and headache in few people	N	NA
Curcumin	Constituent of the spice turmeric	A1;B2	NA	5 g/day	NA	N	NA
Gingko Biloba	Herbal product	A1	Modulating cerebroelectrical activity	120 – 600 mg	NA	N	NA
Ginseng	Roots, stems and leaves of the Ginseng plant	A2;A5	Modulating cholinergic, glutaminergic, and other molecular signalling pathways	200 - 600 mg	NA	N	NA
Glucose	Breakdown of complex sugars, carbohydrates	A1;A3; B1;B2	Prime source of fuel of the CNS; modifying neural metabolism and neural activity; influencing the synthesis of neurotransmitters	25–50 g	Well tolerated	Y	Not prohibited
Guarana	Seeds of the guarana plant (*Paullinia cupana*); artificial sources such as energy-drinks	A1;A3;A5	NA (high content of caffeine, similar effects and mechanisms suggested)	75 mg	Well tolerated if guidelines for caffeine intake are respected	N	NA
L-Carnitine	Natural sources such as meat; dietary supplement or energy-drinks	A1	NA	NA	NA	N	Not prohibited
L-Theanine (+ Caffeine)	Green tea	A1;A2;A3	Antagonist effect on group 1 metabotrophic glutamate receptors	100 mg of L-theanine + 50 mg of caffeine	Well tolerated	Y	NA
n-3 Polyunsaturated Fatty Acids	Natural sources such as fish products (sardines, salmon, tuna, seafood, krill), some plants, nut oils	A1;A4; A5;B1	DHA and EPA generate neuroprotective metabolites, EPA increases serotonin release by reducing E2 series prostaglandins; DHA influences serotonin receptor action by increasing cell membrane fluidity	NA	Well tolerated	N	NA
P-Synephrine	Bitter oranges	A1;A3	Sympathomimetic properties	20–100 mg	NA	N	NA
Rhodiola Rosea	Herbal product	A2;A5	Normalises the release of stress hormones; activation of ATP synthesis in mitochondria	270 mg	Well tolerated	N	NA
Theacrine (+ Caffeine)	Synthetic compound similar to caffeine	A2;A3;B2	Adenosine receptor antagonist	150mg CAF + 125mg TCr	NA	Y	NA
Tyrosine	High-protein food products (chicken, turkey, fish, milk, yogurt,…)	A2;A4	Precursor to the catecholamine neurotransmitters DA and NA	150 mg/kg	NA	Y	Not prohibited

(*) Enough evidence supporting its use in order to improve mental energy in athletes?

NA- Not Available Y- Yes N- No

A1- Boost of the overall cognitive functions: learning, memory, creativity, intelligence
A2- Anxiety and stress reduction before competitions or exercises
A3- Improvement of the degree of attention and concentration, to increase the probability of success and decrease the risk of injury
A4- Improvement of mood to get more motivation
A5- Reduction of the perception of fatigue, as this one increases the likelihood of losing strength, concentration and motivation which leads to an increased risk of injury
B1- Help providing adequate energy to maintain muscle function, considering exercise speed (sprint over short distances) or long duration (marathon)
B2- Ameliorate recovery after training or competition

To conclude, we were able to confirm our initial hypothesis «It is presumed that nootropics can help improving the development of cognitive abilities reaching a higher performance in the sports field». Nevertheless, in view of the current evidence, this statement is only applicable to a few compounds (7) such as: *Caffeine; Cannabidiol; Glucose; L-Theanine (+ Caffeine); Rhodiola Rosea; Theacrine (+ Caffeine); and Tyrosine*. Other compounds (3) seem to play key roles in the cognitive performance but may not be necessary for athletes as a supplement, as they have shown to be effective only in cases of deficiency or mental impairment such as: *B group Vitamins; n-3 PUFAs; Curcumin.* Finally, the following compounds(8) need further research as they seem to have a potential role to improve athletes' performance but there is no clear evidence yet to support its use for the considered purpose: *BCAA, CDP-Choline, Creatine; Gingko Biloba; Ginseng; Guarana; L-carnitine; P-synephrine*.

DISCUSSION

A growing number of safety and ethical concerns of smart drug use by healthy people have been raised. *Safety concerns* are mainly the online purchase medication from unregulated manufacturing sources and the lack of data about the danger from cognitive enhancers -as some drugs being sold have no published clinical trials on their safety and efficacy-. Furthermore, longitudinal data on cognitive enhancing drug use by healthy people using rigorous survey methodology are needed, and the acquisition of this kind of products should be strictly regulated.[103,104] An *ethical concern* related to the use of these substances by elite athletes is that it can be considered by many as cheating or acting against the *fair game* principles.

Most nootropics are legal as they are classified as *dietary supplements*, which are regulated as foods. Moreover, the legal status of a particular nootropic may not universally apply to other nation's regulatory codes. *Herbs and Herbal Extracts* and *Dietary Nootropic Nutrients* are apparently legal across the world, while *Synthetics* (from inorganic sources) and *Semi-Synthetics* (from natural sources) are regulated differently depending on the country.

Regarding elite sports, the *World Anti-Doping Agency* (WADA) elaborates every year a *Prohibited List* serving as the international standard for identifying substances and methods prohibited in sport. In Spain, is the AEPSAD who regulates the normative. From the drugs reviewed in this study, most of them are allegedly legal and safe, as they are natural compounds, herbal products or dietary supplements. Especially to mention is *Cannabidiol* (CBD), as it is no longer prohibited yet products extracted from cannabis plants contain varying concentrations of THC, which remains a prohibited substance and could cause a positive anti-doping test. As such, the use of any CBD product is at the athlete's own risk.

Given these findings, we encourage future studies exploring potential nootropics in terms of effectiveness, mechanisms of action and safety. Moreover, it is fundamental to employ quantitative analytical techniques, including the use of consensus questionnaires and assessments– such as the AMES-, trials including randomization and placebo and/or dose-effect response expectancy, and post-hoc analysis to gain a greater understanding how expectancy is modulated, and more importantly, how they may influence sport and cognitive performance.

With a drug and dietary supplement market growing massively, marketing and trending pushes athletes and coaches -with little knowledge on the topic- to use and recommend supplements with no scientific backup. Furthermore, from the authors' point of view, there are more important issues that should be considered before deciding to use any supplements, as some athletes may be looking for help in nootropics to improve their performance, although they are failing at other basic principles of lifestyle and nutrition. As an example, evidence to date supports the fact that *sleep* is important for optimal athletic performance, yet many elite athletes do not experience optimal sleep quality or quantity and, from a cognitive perspective, this may have implications for reaction time, memory, learning, and mood.[105]

In addition, evidence is clear about the fact that bad habits such as smoking, and alcohol consumption have negative effects on the mental functions. Given the large availability of nicotinic acetylcholine receptors throughout the brain, and the wide range of neurotransmitter systems affected (norepinephrine, serotonin and dopamine), *nicotine* influences a wide variety of cognitive domains such as sensorial, motor, attention and alertness, executive function, learning and memory.[106,107] Alcohol intake is also related to cognitive impairment—for example, in spatial cognition, short-term memory, and reference memory.[108]

It is also worth mentioning the possible role of the *gut-brain axis*. Although it remains poorly explored, consistent evidence seems to affirm certain diets such as the high processed-meat containing, and potentially the amounts and types of bacteria in the gut may contribute to disorders that affect the brain, as «the microbiota affects neurons and microglia in the brain through metabolites that are released into the circulation» as Chu and colleagues[109] suggested. It is hypothesized that changes in the microbiota lead to altered gene expression in brain cells resulting in alterations in the behaviour in response to changing environmental cues. [110,111]

Therefore, the following pyramid (**Fig. 5**) is proposed with the aim of putting in perspective the place we believe nootropics should occupy within the whole framework of nutrition and lifestyle of the athletes.

Fig. 5. ***Pyramid of nutrition and lifestyle for athletes.*** Inspired by the *Muscle & Strength Nutrition Pyramid.* Helms, E. 2019

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