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# NOOTROPICS: EFFECTS ON BRAIN PLASTICITY AND COGNITIVE FUNCTIONS

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***SUMMARY***

*Nootropics represent a heterogeneous group of substances that affect cognitive functions primarily through modulation of neuroplasticity. Classic agents improve neuronal metabolism and, in experimental models, increase neurotrophin levels, but their clinical efficacy in dementia and other cognitive disorders remains moderate. Psychostimulants provide short-term improvement in attention and performance; however, they do not strengthen long-term plasticity and may adversely affect the developing brain. Herbal and nutraceutical agents exert mild and delayed effects, predominantly manifesting in individuals with mild cognitive complaints or deficits. Despite growing interest in pharmacological cognitive enhancement, convincing evidence of a clinically meaningful improvement in cognitive functions in healthy individuals is lacking, whereas the strongest effects on neuroplasticity continue to be demonstrated by non-pharmacological interventions.*

***KEYWORDS:*** *neuroplasticity; cognitive enhancement; nootropic drugs; memory; attention; nootropics.*

***CONFLICT OF INTEREST***. The authors declare no conflict of interest.

# *НООТРОПЫ: ВЛИЯНИЕ НА ПЛАСТИЧНОСТЬ МОЗГА И КОГНИТИВНЫЕ ФУНКЦИИ*

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***РЕЗЮМЕ***

*Ноотропы представляют собой разнообразные вещества, влияющие на когнитивные функции преимущественно через модуляцию нейропластичности. Классические препараты улучшают метаболизм нейронов и в экспериментальных моделях повышают уровень нейротрофинов, но их клиническая эффективность при деменции и других когнитивных нарушениях остаётся умеренной. Психостимуляторы дают кратковременное улучшение внимания и работоспособности, однако не усиливают долговременную пластичность и могут неблагоприятно влиять на развивающийся мозг. Растительные и нутрицевтические средства оказывают мягкое и отсроченное действие, преимущественно проявляясь у лиц с легкими когнитивными жалобами или дефицитами. Несмотря на растущий интерес к фармакологическому когнитивному усилению, убедительных данных о значимом улучшении когнитивных функций у здоровых людей нет, а наиболее выраженный эффект на нейропластичность продолжают демонстрировать немедикаментозные вмешательства.*

***КЛЮЧЕВЫЕ СЛОВА:*** нейропластичность; когнитивное усиление; ноотропные препараты; память; внимание; ноотропы.

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## Introduction

The normal functioning of cognitive processes largely depends on the brain's capacity for neuroplasticity — structural and functional changes in neural networks under the influence of experience and learning. Since the mid-20th century, attempts have been made to pharmacologically improve memory and other cognitive functions. The term "nootropic" was introduced in 1972 by the Romanian chemist C. Giurgea to describe substances that enhance higher brain functions (thinking, learning, memory) without producing stimulation or sedation. Classic nootropics are considered to be pyrrolidone derivatives (piracetam), first synthesized in the 1960s; Giurgea formulated the criteria for a nootropic as follows: enhancement of learning and memory, increased resistance of the brain to damaging influences, and minimal toxicity and side effects. Initially, these drugs were developed forthe treatment of cognitive disorders — dementia, consequences of traumatic brain injury, stroke, and so on.

In recent years, however, there has been an emerging phenomenon of nootropic and stimulant use by healthy individuals (students, knowledge workers) for the purpose of pharmacological cognitive enhancement. Different studies report a wide range of prevalence — from a few to tens of percent — depending on the population and definitions used.

For example, surveys among students have found at least a single use of prescription stimulants (modafinil, methylphenidate, amphetamines) in 1–5% of respondents in European countries, whereas anonymous survey methods show figures up to ~20%. At the same time, the majority — up to 80–90% — of young people do not express interest in such interventions [1–3].

The high demand for "brain improvement" has driven rapid expansion of the market for dietary supplements and products marketed as "smart drugs." More than 100 products are available on online markets, promising to improve memory, attention, creative thinking, and so forth. However, many of them are either poorly studied or fail to demonstrate significant effects under rigorous testing. Ethical issues and concerns about fairness are actively discussed in the context of cognitive enhancement in healthy people. In 2016, the American Medical Association officially opposed prescribing nootropic drugs to healthy individuals because of the uncertain benefit–risk balance.

An integral part of this discussion is the question of how nootropics affect the brain itself — particularly plasticity processes. On the one hand, many nootropics were designed to support neuroplastic changes (restoration of neuronal connections after injury and in dementia). On the other hand, there are concerns that artificially boosting cognitive productivity may come at a "cost" to neuroplasticity — for example, by reducing the natural capacity for adaptive learning or redistributing brain resources. Some reviews have noted that stimulant use at a young age may impair behavioral flexibility and increase vulnerability to addictions by affecting the development of the dopaminergic and glutamatergic systems [4].

**The aim** of this review is to summarize current scientific data on the effects of different types of nootropic agents on (a) brain plasticity (synaptic and structural) and (b) cognitive functions (memory, attention, executive functions) in humans. The review includes both classic nootropics with predominantly metabolic actions and stimulants and herbal preparations that are frequently referred to as nootropics. We separately consider the proposed mechanisms of action of these agents in the context of neuroplasticity and their actual efficacy according to controlled trials.

## Neurobiological mechanisms of nootropics and their effects on brain plasticity

### Classic nootropics

The first nootropic, piracetam, was synthesized in 1964 and is still used in a number of countries for the treatment of cognitive impairment. Despite its long history, its exact mechanism of action remains incompletely understood. It is known that piracetam is neither a stimulant nor a sedative and does not exert a direct effect on classical neurotransmitter receptors. Its main actions consist in improving cerebral energy and neurotransmitter metabolism: piracetam and related compounds (aniracetam, oxiracetam, phenylpiracetam, etc.) enhance the utilization of glucose and oxygen by brain tissue, have antihypoxic properties, reduce platelet aggregation, and improve blood rheology in microvessels. Experimental studies have demonstrated increased synthesis of membrane phospholipids and proteins important for synaptic plasticity.

Piracetam has been shown to restore age-related declines in the fluidity of brain cell membrane lipids, which may facilitate receptor function and improve signal transmission. This property is linked to improved neuroplasticity — the ability of neurons to form new connections and maintain long-term potentiation (LTP). In addition, piracetam has demonstrated neuroprotective effects in vitro — it reduces neuronal damage induced by β-amyloid, stimulates mitochondrial function, and attenuates oxidative stress [5].

In animal studies, nootropics frequently enhance molecular markers of plasticity. For example, a combination of Ginkgo biloba and ginseng extracts increased hippocampal levels of synaptophysin and the NR2B subunit of the NMDA receptor — proteins associated with synapse formation. Noopept (a peptide nootropic developed in Russia) acutely increased expression of neurotrophin genes BDNF and NGF in the rat hippocampus. With course administration (28 days), the effect persisted and even intensified, without development of tolerance. This was accompanied by improvements in learning performance and served as a rationale for considering noopept as a promising agent for early-stage Alzheimer's disease prevention. Thus, some classic nootropics can activate intracellular pathways leading to neurotrophic effects and enhanced neuronal plasticity [6].

It should be emphasized that clinical evidence for the efficacy of traditional nootropics is limited. Early small-scale trials often reported improvements in subjective or behavioral measures in patients with cognitive impairment treated with piracetam and other agents. For instance, a meta-analysis of 19 RCTs with piracetam reported a statistically significant global improvement in older adults with dementia or mild cognitive impairment, with a number needed to treat (NNT) of about 7 [7]. However, in those same studies it was not possible to demonstrate consistent benefits on specific neuropsychological tests. Review authors pointed out that the methodological quality of many trials was suboptimal (small samples, missing data from the first phase of crossovers, etc.). A Cochrane Review (2001, updated 2004) concluded that available data do not support the use of piracetam in dementia and that more rigorous trials of ≥6 months are required [8].

Overall, classic nootropics appear to create a favorable metabolic milieu for neuroplastic processes (protecting neurons from hypoxia and damage, improving trophic support and neurotransmitter balance). This may not be sufficient to produce a noticeable cognitive benefit in the absence of concurrent training or rehabilitation, but such agents may potentiate the effects of non-pharmacological interventions, such as cognitive training.

### Neuromodulators and stimulants

Another major group of substances used as cognitive enhancers consists of drugs that modulate neurotransmitter levels (primarily monoamines) in the brain. These include psychostimulants: amphetamines (mixed amphetamine salts), methylphenidate, and modafinil. In medical practice, they are

used to treat attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and several other conditions. In healthy individuals, these drugs can indeed produce feelings of wakefulness, enhance concentration, and increase endurance during monotonous tasks.

Their effects on neuroplasticity, however, are ambiguous. On the one hand, transient activation of dopaminergic and noradrenergic pathways improves functional connectivity in attention and executive control networks, translating into better performance in some tasks. For example, a 2010 meta-analysis showed that methylphenidate significantly improves memory (particularly verbal memory) in healthy subjects [9]. Modafinil, in turn, maintains performance, vigilance, and working memory in sleep-deprived volunteers better than placebo. In well-rested individuals, the effect of modafinil is more selective: simple cognitive tests often show no benefit, whereas in complex and novel tasks there may be improvements in attention and executive functions.

At the same time, in most studies stimulants do not enhance creative thinking or cognitive flexibility in healthy individuals; indeed, some reports describe a reduction in divergent thinking under modafinil. A likely explanation is "overloading" of the dopamine–noradrenaline system: excessive focus and hyper-concentration may impair spontaneous associations and strategic flexibility [10].

Long-term psychostimulant use may induce adaptive changes in neural circuits. Animal studies show that chronic methylphenidate administration during the juvenile period disrupts normal maturation of the prefrontal cortex, with reduced behavioral flexibility and a tendency toward more stereotyped learning strategies. Urban and Gao (2014) hypothesized that artificially maintaining high levels of dopamine and glutamate for cognitive enhancement may interfere with normal plastic re-learning processes and increase the risk of addictive behavior [4]. Their review emphasizes that stimulants improve performance on familiar tasks but do not enhance the acquisition of new complex skills and, at high doses or in childhood, may even impair it. In other words, acute cognitive "doping" via stimulation is not equivalent to genuine development of cognitive potential.

From the standpoint of synaptic plasticity, ampakines — experimental nootropics that potentiate AMPA receptor activity — are of particular interest. They directly increase synaptic transmission and, as shown in animal models, can enhance BDNF production in the brain. In a Huntington's disease model, a short course of the ampakine CX929 normalized BDNF levels in the hippocampus, restored actin-dependent structural synaptic changes, and rescued impaired LTP, accompanied by memory improvement in mice [11]. Importantly, these effects were achieved within a few days without major adverse events. Ampakines are considered a promising avenue for activating intrinsic plasticity and memory resources without systemic stimulant effects. None has yet been approved for clinical use, but safety studies are ongoing.

In summary, psychostimulants and neuromodulators exert pronounced short-term effects on neurochemistry that can enhance certain cognitive functions (attention, reaction speed, working memory) in healthy individuals. These effects are confined to an optimal dose range; beyond this, performance worsens according to an inverted U-shaped dose–response relationship. Their contribution to long-term neuroplasticity is doubtful: rather than promoting the formation of new neural connections, they transiently mobilize existing resources. Moreover, concerns remain about potential adverse consequences for plasticity with misuse, particularly at a young age. Clinicians therefore recommend caution with the use of prescription stimulants in healthy individuals, and in children they should be prescribed strictly for ADHD, taking into account the high plasticity of the developing brain and the possibility of long-term consequences.

**Herbal nootropics and natural compounds**

A substantial share of agents marketed as nootropics consists of natural products (for example, plant extracts). Historically, many medical traditions have used herbs to "calm the nerves" and improve memory. Modern studies of some of these products have shown modest cognitive effects, although the quality of evidence is often limited. The most well-known examples include:

- **Ginkgo biloba.** Standardized Ginkgo biloba leaf extract (EGb 761) is one of the most popular phytotherapeutic agents for memory. Meta-analyses have shown that in patients with dementia, 22–24 weeks of Ginkgo biloba treatment (120–240 mg/day) produce small improvements in cognitive scores and everyday functioning compared with placebo. A 2017 overview noted that Ginkgo may be more effective with long-term use (>5 months) and at doses ≥200 mg. Mechanisms include antioxidant effects, improved cerebral blood flow, and neurotrophic activity — in animal studies, chronic Ginkgo administration increased BDNF levels. Data in healthy individuals are inconsistent: some studies reported slight improvements in processing speed and attention in young volunteers, whereas others found no effect. The effect is probably more pronounced in those with age-related changes. Ginkgo is generally safe but may increase bleeding risk (due to antiplatelet action), so concomitant use with aspirin is undesirable [12].
- **Bacopa monnieri.** An Ayurvedic "brain tonic" traditionally used for fatigue and forgetfulness. Its extracts contain bacosides with antioxidant and neuroprotective properties. Modern RCTs have mostly been conducted in older adults with mild cognitive complaints. A meta-analysis of 9 trials (518 participants) showed that ≥12 weeks of bacopa treatment significantly accelerated information processing (e.g., reduced Trail Making Test-B completion time and choice reaction time). Memory improvements were less consistent, likely due to variability of methods. Some RCTs showed better verbal recall and reduced anxiety with bacopa, but gastrointestinal side effects (nausea, dyspepsia) were more common than with placebo. Overall, bacopa is considered a relatively safe herbal agent with modest nootropic effects upon prolonged use (from 2–3 months), primarily enhancing attention and stress resilience [13].

- **Ginseng (Panax ginseng)**. In traditional Chinese medicine, ginseng is used to "strengthen vital energy," including mental functions. Some studies have shown that a course of Asian ginseng (e.g., 400 mg of G115 extract) can improve working memory and subjective well-being in healthy volunteers. Combined use with Ginkgo (e.g., fixed combinations) improved some cognitive test scores after stroke and in dementia, presumably via synergistic effects on the cholinergic system and neurotrophins. However, large independent studies are lacking, and ginseng's impact on cognitive plasticity remains hypothetical. Ginseng may have a tonic effect (activating the HPA axis and neurotransmitter systems), but specific neuroplastic effects (such as neurogenesis) require confirmation [14].
- **Ashwagandha (Withania somnifera)**. An Indian adaptogen known for its anxiolytic and cortisol-lowering properties. In the cognitive domain, small RCTs have shown that ashwagandha (300–600 mg/day of root extract) improves memory and attention in patients with mild cognitive impairment and in healthy individuals with memory complaints. It is assumed that by reducing anxiety and oxidative stress, ashwagandha creates a more favorable milieu for learning. Experimental studies indicate that it stimulates neurite outgrowth and increases antioxidant enzyme levels in the brain. Ashwagandha is viewed as a promising natural agent, but larger trials are needed [14].
- **Caffeine and other naturally occurring CNS stimulants.** Caffeine is the most widely used psychostimulant and can be considered a situational "nootropic": it acutely increases alertness, reaction speed, and short-term concentration. In combination with L-theanine (an amino acid from tea), caffeine more effectively enhances attention and reduces distractibility than either substance alone. However, these effects are transient, tolerance develops, and high doses cause anxiety and tremor. Theobromine (from cocoa) and nicotine can also transiently improve attention and mood, but because of health risks they are not regarded as acceptable cognitive enhancers. Microdosing of psychedelics (LSD, psilocybin) is currently being discussed as a potential way to enhance creativity and emotional plasticity, as these compounds have been shown to increase neurotrophin levels (BDNF) and synaptogenesis in neuronal cultures. Nonetheless, clinical evidence for cognitive benefits of microdosing is extremely limited, and this approach remains experimental [15].

In general, natural nootropics are characterized by mild effects and a slower onset of action. For instance, a single dose of Ginkgo or bacopa will not immediately improve memory; accumulation and potential neurometabolic shifts over weeks are needed. This contrasts with pharmacologic stimulants (caffeine, amphetamines), whose effects appear within hours. From the perspective of plasticity, it can be assumed that indirect antioxidant and vasotropic actions of herbal nootropics create conditions that support plastic processes — such as protecting neurons from chronic stress and inflammation. Course administration of omega-3 fatty acids and antioxidants, for example, has been associated with higher neurotrophin levels and improved synaptic plasticity in several models of neurodegeneration. In healthy individuals, however, the contribution of nutraceuticals to supranormal cognitive enhancement is minimal. Non-pharmacological factors — such as physical exercise, which robustly increases BDNF and improves memory via hippocampal neurogenesis — have far stronger "nootropic" effects in a healthy brain [16].

**Efficacy of nootropics: clinical outcomes and limitations of the evidence**

**In patients with cognitive impairment**

Despite decades of research, no nootropic drug has become a "breakthrough" treatment for dementia or other cognitive disorders. The most effective pharmacotherapeutic strategies in dementia are not classic nootropics but cholinergic agents (cholinesterase inhibitors — donepezil, galantamine) and the partial NMDA antagonist memantine. They provide moderate symptomatic improvement in Alzheimer's disease but their effect diminishes as neurodegeneration progresses.

In the search for adjunctive agents to support cognitive function, classic nootropics have been investigated. Some studies report that combining cholinesterase inhibitors with cholinergic nootropics (e.g., citicoline or alpha-GPC) may yield better cognitive outcomes than cholinesterase inhibitor monotherapy, though data are inconsistent. A 2017 systematic review concluded that in patients with dementia, Ginkgo biloba extract (EGb 761) at 240 mg/day provides cognitive and behavioral improvements comparable to those of cholinesterase inhibitors, and combination therapy may offer additional benefits [17].

In vascular cognitive impairment, piracetam and cerebrolysin (a mixture of neuropeptides) demonstrated small positive effects in some trials, but methodological issues preclude firm recommendations. In post-stroke cognitive dysfunction, cerebrolysin has been assigned level II evidence (probable efficacy) based on several RCTs and a meta-analysis, whereas piracetam did not significantly influence cognitive recovery after stroke [18].

Overall, in clinically overt cognitive impairment, nootropics may provide modest support but do not replace disease-specific therapies. Their effects are most noticeable in mild and early-stage disorders, while they are ineffective in advanced dementia.

**In healthy individuals**

The question of efficacy in healthy people is particularly controversial. On one hand, widespread self-experimentation with pharmacological enhancers suggests that many individuals subjectively perceive benefits. On the other hand, placebo-controlled trials often show either no effect or very small improvements that do not always reach robust statistical or clinical significance.

For example, a randomized placebo-controlled experiment by Repantis et al. (2021) involving 48 healthy men compared single doses of methylphenidate, modafinil, caffeine, and placebo using a battery of cognitive tests. Only a few improvements were detected: methylphenidate improved delayed recall after 24 hours and reduced subjective fatigue; caffeine enhanced performance in a sustained attention task. Modafinil did not produce significant benefits on any outcome in this sample [19]. At the same time, participants frequently overestimated the degree of improvement under stimulants. This "illusory productivity" effect has been documented for modafinil: subjects reported feeling more productive, although objective measures (except for preventing sleepiness) did not support such impressions. This overestimation may be risky, as individuals may make errors under nootropics due to excessive self-confidence.

Summarizing these data, the most consistent effects in healthy individuals are:

- Stimulants: improve performance under fatigue or sleep deprivation. Modafinil is recognized as an effective countermeasure against cognitive consequences of prolonged wakefulness (e.g., in shift workers or military personnel on extended missions). In well-rested individuals, its benefits are mostly seen in complex tasks requiring integration of multiple cognitive functions. Methylphenidate substantially improves concentration and processing speed, particularly in individuals with lower baseline attention. Caffeine reliably increases alertness and reduces reaction time but does not improve higher-order reasoning or memory for complex structured material.
- Nootropic nutraceuticals: act in the long term. For example, several months of DHA (omega-3) supplementation can enhance attention in young individuals with low baseline omega-3 intake by optimizing membrane processes in neurons. B-vitamins can improve memory performance in the context of deficiency. Nonetheless, in well-nourished healthy people, such supplements do not show effects beyond normalization. Bacopa, after 2–3 months, improves some memory parameters in adults, as demonstrated in several small RCTs (~300 participants in total). Lion's mane mushroom (Hericium erinaceus), which stimulates NGF synthesis, improved cognitive functions in older adults with MCI in a pilot study at 4 g/day for 4 months [20]. All these findings, however, require confirmation in larger trials.

**Conclusion**

Neuroplasticity — the basis of learning and memory — remains a complex target for pharmacological modulation by nootropics. To date, evidence has accumulated that some nootropic drugs can modulate brain plasticity: classic nootropics (piracetam and analogues) improve cellular metabolism and may increase expression of neuronal growth factors, while experimental agents (ampakines, noopept) can more directly enhance synaptic plasticity via regulation of BDNF and NGF [5, 6, 11, 16]. This supports the possibility of pharmacologic support of cognitive functions in brain injury and neurodegenerative processes. In clinical practice, nootropics have found limited use as part of combination therapy for mild to moderate cognitive impairment, but their effects are generally modest compared with core treatments such as cholinesterase inhibitors [17, 18].

In healthy individuals, nootropic substances do not produce dramatic increases in intelligence. Objective improvements are usually limited to acceleration of simple cognitive operations or increased alertness under specific stress conditions (sleep deprivation, fatigue) [9, 10, 19]. More complex functions — creative thinking, acquisition of new complex skills — are weakly or not at all enhanced pharmacologically; for these, intrinsic plasticity, which cannot be substituted by a "pill," appears to be more important. There is also evidence of potential harm: inappropriate use of stimulants may decrease intrinsic motivation to learn without pharmacologic support, foster psychological dependence, and shift emphasis from long-term skill development to short-term performance. Side effects (insomnia, anxiety, cardiovascular strain) can further negate benefits. Herbal nootropics and nutritional supplements are generally safer, but their efficacy often approximates placebo; exceptions include deficiency states (e.g., vitamins, omega-3), where supplementation restores normal function rather than enhancing it beyond baseline.

At present, there is no "magic pill" that reliably and safely boosts cognitive abilities above baseline in healthy individuals. The most effective strategies for improving memory and brain plasticity remain non-pharmacological interventions — cognitive training, education, physical exercise, and adequate sleep. These factors have strong evidence for increasing neurotrophins (such as BDNF with exercise) and enhancing neural connectivity, providing the foundation for sustained cognitive growth [16]. Pharmacologic nootropics may serve as adjuncts in clinical contexts (post-stroke, after TBI, in early dementia) or in specific short-term situations (night shifts, high-stakes operations), but their use should be carefully evaluated in terms of benefit–risk ratio.

The medical community emphasizes the need for further research: first, on the long-term effects of nootropics on the healthy brain (including developmental processes in youth); and second, on the discovery of new agents that more selectively enhance neuroplasticity without resource depletion. Advances in molecular neurobiology — such as gene therapy and neurotrophic factor — based interventions — may open new horizons for cognitive enhancement in the future. For now, claims about "miraculous" nootropics should be treated with caution: cognitive improvement is a complex, multifactorial process, and pharmacology represents only one of many influences.

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