



Cognitive enhancement

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Cognitive enhancement refers to the improvement of cognitive ability in normal healthy individuals. In this article, we focus on the use of pharmaceutical agents and brain stimulation for cognitive enhancement, reviewing the most common methods of pharmacologic and electronic cognitive enhancement, and the mechanisms by which they are believed to work, the effectiveness of these methods and their prevalence. We note the many gaps in our knowledge of these matters, including open questions about the size, reliability and nature of the enhancing effects, and we conclude with recommendations for further research. © 2013 John Wiley & Sons, Ltd.

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INTRODUCTION

Cognitive enhancement refers to the improvement of cognitive ability in normal healthy individuals.^a There are many ways to boost levels of cognitive ability, including engaging in physical exercise¹ and meditating.² However, the term ‘cognitive enhancement’ is usually used in connection with interventions applied more directly to the brain: pharmaceutical agents and brain stimulation. In this article, we will focus on these neurotechnological methods for cognitive enhancement, which have attracted great public interest in recent years and a growing number of users. We begin the review by surveying the most common methods of pharmacologic and electrophysiologic cognitive enhancement and the mechanisms by which they may work. We then review what is known about the effectiveness of these forms of enhancement and their prevalence, noting the many gaps in our knowledge of these matters. We conclude with recommendations for further research and policy.

THREE CLASSES OF DRUGS WITH COGNITIVE ENHANCEMENT POTENTIAL

Potential pharmacologic cognitive enhancers include a variety of drugs developed to treat cognitive dysfunction. That is, these drugs were developed with the goal

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of moving cognitively impaired individuals upward on the ability scale toward a normal level. These same drugs have been used as cognitive enhancers by normal individuals in an attempt to achieve ‘better than normal’ cognitive ability. Although many different substances have been used for this purpose,³ three well-known classes of drug in current clinical use will be discussed here: the traditional stimulants, primarily used to treat Attention Deficit Hyperactivity Disorder, the acetylcholinesterase inhibitors, used to treat Alzheimer’s disease, and modafinil, a novel stimulant primarily used to treat narcolepsy.

Stimulants

Stimulants include methylphenidate, best known as Ritalin or Concerta, and amphetamine, most widely prescribed as mixed AMP salts consisting primarily of dextroamphetamine (d-AMP), known by the trade name Adderall. These medications have become familiar to the general public because of the growing rates of diagnosis of ADHD children and adults^{4,5} and the recognition that these medications are effective for treating ADHD.^{6,7}

Methylphenidate and amphetamine affect the catecholamines dopamine and norepinephrine, which are key neurotransmitters in the cortical and sub-cortical systems that enable us to focus and flexibly deploy attention.⁸ The therapeutic effect of these drugs for ADHD is consistent with the finding of abnormalities in the catecholamine system in patients with ADHD (e.g., Ref 9). Both drugs exert their effects on cognition primarily by increasing levels of catecholamines in prefrontal cortex and the cortical

and subcortical regions projecting to it, and this mechanism is responsible for improving attention in ADHD.^{10,11} Cognitive enhancement use of stimulants is aimed at improving the same attentional systems in normal, healthy people.

Acetylcholinesterase Inhibitors

Another class of drugs with enhancement potential is the acetylcholinesterase inhibitors, widely used for the treatment of mild to moderate Alzheimer's disease. These drugs, including donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne), increase levels of the neurotransmitter acetylcholine in the brain by decreasing the activity of the enzyme that normally breaks down acetylcholine. Degeneration of cholinergic neurons is a central factor in the cognitive decline of Alzheimer's disease. More generally, acetylcholine plays a broad role in normal cognition¹² and might therefore be target for pharmacologic cognitive enhancement.

Modafinil

Modafinil, marketed as Provigil, was originally developed for the treatment of daytime sleepiness in patients suffering from narcolepsy, and is now approved by the US FDA for sleepiness associated with sleep apnea and shift-work sleep disorder. In addition to improving subjective feelings of energy and alertness in sleep-deprived individuals, it improves their cognitive performance on objective tests.¹³ Some studies have found cognitive enhancing effects in normal subjects who are not sleep deprived.¹⁴ In addition to its use for the three FDA-approved indications it has been prescribed off-label for a much wider range of indications, including depression, attention deficit hyperactivity disorder and jet lag.¹⁵

Its mechanism of action is different from the traditional stimulants, which have also been used to counteract the effects of sleep deprivation, but much remains to be understood about how it works. In addition to affecting dopamine and norepinephrine, it is also believed to affect gamma-aminobutyric acid, glutamate, histamine and orexin/hypocretin.¹⁵ Enhancement use of modafinil involves staving off the cognitive decline associated with sleep deprivation and additionally the possibility of subtle cognitive improvements in well-rested individuals.

BRAIN STIMULATION FOR COGNITIVE ENHANCEMENT

The literature on noninvasive brain stimulation has grown rapidly since the turn of the century. Transcranial magnetic stimulation (TMS) and transcranial

direct current stimulation (tDCS) are the two most commonly employed methods available for use in humans. Each was explored by scientists initially as a research tool for studying brain function, although more recently the therapeutic and enhancement potential of these methods has also been explored.

TMS utilizes electromagnetic induction and involves the generation of a rapid time-varying magnetic field in a coil of wire. When this coil is held to the head of a subject, the magnetic field penetrates the scalp and skull, inducing a small current parallel to the plane of the coil in the brain that is sufficient to depolarize neuronal membranes and generate action potentials. Different TMS paradigms employ a variety of pulse frequencies, intensities, and stimulation locations to achieve specific diagnostic, therapeutic, and experimental effects. Repetitive TMS (rTMS)—which involves the application of a series of pulses that is presented at a predetermined frequency (typically > 0.3 Hz)—is especially germane to cognitive enhancement because it can produce effects that outlast the application of the stimulation. Evidence suggests that rTMS delivered at a low frequency (0.5–2 Hz) tends to focally decrease cortical excitability, whereas higher frequencies (faster than 5 Hz) tend to increase excitability.¹⁶ Because the spatial resolution of TMS is fairly high (1 cm² at the cortical surface), investigators typically identify stimulation targets carefully using scalp landmarks (e.g., the 10–20 system used for EEG electrode placement), functional localizers (e.g., using evoked motor responses to locate the region of the motor cortex that represents specific hand muscles), or MRI-guided neuronavigational systems.¹⁷ While studies in normal individuals have only demonstrated transient changes in cognition and behavior, limited evidence from TMS studies in patient populations suggests that repeated administration of TMS can lead to enduring changes in behavior, presumably due to persistent changes in patterns of neural activity (e.g., Refs 18, 19). TMS is currently being explored experimentally as a therapy for a variety of conditions including but not limited to motor and cognitive deficits after stroke, movement disorders, Alzheimer's disease, epilepsy, migraines, and tinnitus (see Ref 20 for a review). Since 2008, TMS has been approved by the US FDA as a therapy for depression, and is currently being provided by mental health professionals across the country (<http://www.neurostartms.com>).

Transcranial direct current stimulation (tDCS) involves the application of small electrical currents to the scalp through two surface electrodes. Unlike TMS, which induces currents of sufficient magnitude to stimulate action potentials, the weak electrical currents

employed in tDCS (typically 1–2 mA) are thought to alter the resting membrane potentials of neurons incrementally, affecting the likelihood of firing of cortical neurons over time. The effects of tDCS depend on the polarity of the electrode applied to the scalp: cathodal stimulation is associated with decreased cortical excitability due to hyperpolarization of cortical neurons, while anodal stimulation is associated with increased cortical excitability due to subthreshold depolarization. These effects may last for minutes to hours depending on the intensity, polarity, and duration of stimulation.^{21,22} Stimulation is typically administered using relatively large (25 cm² or 35 cm²) pads that are moistened with saline to facilitate electrical conduction, although systems that use smaller electrodes for ‘high-definition’ stimulation are becoming more widely available.²³ The area of brain stimulated during conventional tDCS is presumed to be more diffuse than that stimulated using TMS, which generally obviates the need for image-guided neuronavigational systems. Given its ease of administration, versatility, and minimal side effects, there has recently been an upsurge of interest in the use of tDCS for both research and clinical purposes. Direct current stimulation is being explored as a therapy for many of the same conditions as TMS, including but not limited to stroke recovery, mood and anxiety disorders, chronic pain, and Parkinsonism. tDCS has not yet been approved by the FDA for any therapeutic indication, and treatments are therefore considered ‘off-label’ applications of this technology (see Ref 24 for a review). In addition to tDCS, other electrical brain stimulation techniques are emerging as potentially promising approaches for modulating brain activity. These include transcranial alternating current stimulation (tACS), a technique wherein alternating current is applied through the scalp to the brain in a frequency-specific manner,²⁵ and transcranial random noise stimulation (TRNS), which involves the application of a random electrical oscillation spectrum to the brain.²⁶

EVIDENCE ON EFFECTIVENESS AND SAFETY

Recent discussions in the fields of experimental psychology and clinical trial research have focused on the importance of study power and replication (e.g., Refs 27, 28). It is difficult to assess the effectiveness of current neurocognitive enhancement methods for reasons highlighted in these discussions: Most studies are small and under-powered to find anything but large effects; many studies utilize multiple outcome measures, which further compromises power if correction for multiple comparisons is applied, or

raises the risk of false positive results if no correction is applied, and of course none of the studies are registered in advance so there is no way to know how many null results have gone unreported. These challenges afflict virtually all research in the area of enhancement, including research carried out by highly competent and honest researchers. It seems likely to us that the methods of cognitive enhancement reviewed here have some benefit, for some users, relative to placebo, but how much benefit and for whom is difficult to know given the current state of the research. That research is summarized briefly here.

Effectiveness and Safety of Drugs

All three classes of medication have been reported to enhance performance in certain laboratory cognitive tasks for at least some normal healthy subjects. However, the true reliability and size of these effects, and their usefulness for real-world cognitive enhancement, have not been definitively established. These matters are difficult to determine on the basis of the current literature. Indeed, there is reason to be skeptical concerning the cognitive enhancement potential of these medications.

The largest literature on pharmacologic cognitive enhancement concerns the stimulants. Recent reviews and meta-analyses have found mixed results and some have gone so far as to conclude that the drugs offer no benefit to normal individuals. For example, Chamberlain et al.²⁹ reviewed studies in which CANTAB tasks had been used to assess stimulant effects in patients and healthy control participants. They concluded that ‘acute doses of medication improved aspects of cognition, though findings were more consistent in subjects with ADHD than in healthy volunteers.’ In the words of Repantis et al.³⁰ concerning methylphenidate as well as modafinil, ‘expectations regarding the effectiveness of these drugs exceed their actual effects.’ Hall and Lucke³¹ state that ‘There is very weak evidence that putatively neuroenhancing pharmaceuticals in fact enhance cognitive function.’ An even stronger conclusion was presented by Advokat,³² whose reading of the literature led her to suggest that ‘studies in non-ADHD adults suggest that stimulants may actually impair performance of tasks that require adaptation, flexibility and planning.’ At least two studies have documented paradoxical impairment of cognitive performance by stimulants in certain subsets of people.^{33,34}

We recently surveyed more than fifty experiments on the effects of amphetamine and methylphenidate on a wide array of cognitive functions, including memory (episodic and nonepisodic memory) and executive functions (working memory, cognitive

control) in healthy young adults.³⁵ We discovered a roughly even mixture of significant enhancement effects and null findings. Studies examining stimulants' effects on episodic memory revealed an enhancing effect of stimulants on learning under some circumstances, specifically when the retention interval between study and test was longer than an hour, but not at shorter intervals. The evidence on enhancement of executive functions was much less clear. Although there were many studies reporting significant enhancing effects of stimulants in working memory, there were also many null results. In addition, when significant effects were found, they were sometimes qualified by complex interactions between the order in which participants performed tasks, participants' level of ability on placebo, and participants' genotypes. The same was true of stimulant effects on cognitive control.

In a more recently completed study³⁶ examining the effects of amphetamine on 13 different measures of cognitive performance using a design with sufficient power to detect a medium-size effect in any one measure, we failed to find any evidence of reliable enhancement. Participants in this study did, however, tend to believe their performance was enhanced when on the drug relative to the placebo.

Our finding that participants tended to judge the amphetamine more enhancing than the placebo raises the possibility that it may be the noncognitive effects of stimulants that are most enhancing of work performance. The effects of stimulants on subjective energy, confidence and motivation have been noted by students as being among the helpful effects of amphetamine (cf. Refs 37–39). Military psychologists in the mid-20th century reached similar conclusions about the usefulness of stimulants for enhancing the performance of personnel (see, e.g., Ref 40).

The much smaller literature on the effects of acetylcholinesterase inhibitors on normal cognition was reviewed by Repantis et al.⁴¹ The majority of the studies used donepezil (Aricept) with healthy young or elderly adults, in either single-dose or chronic administrations, and assessed various aspects of learning and memory. Summarizing the mix of null results, positive results and two instances of drug-induced impairment, the authors describe the literature as 'provid[ing] no consistent evidence for a neuroenhancement effect' (p. 480).

Finally, the effects of single doses of modafinil on cognitive ability has been studied with both sleep-deprived and normally rested healthy adults. As mentioned earlier, here is clear evidence of improved executive function and memory for sleep-deprived individuals (e.g., Ref 42). In contrast, with rested adults we find the familiar pattern of positive findings

in certain tasks, for example inhibitory control,¹⁴ but a large number of null results and the occasional finding of impairment (see, e.g., Refs 29, 41, 43).

The safety of pharmacologic cognitive enhancement varies according to the drug used as well as the dosage and frequency of usage. All drugs are widely used therapeutically; their safety profiles in the therapeutic context are well documented and will not be explored in detail here. However, one type of risk should be singled out for comment and that is the risk of dependence.⁴⁴ Stimulants are potentially habit-forming, and nationwide survey analyzed by Kroutil et al.⁴⁵ estimated that almost one in 20 nonmedical users of prescription stimulants meets criteria for dependence or abuse. The risk to individuals using these medications specifically for cognitive enhancement is not known.

Effectiveness and Safety of Brain Stimulation

TMS and tDCS have become important research tools for understanding the neural substrates of cognition in the human brain and have shown promise for a variety of therapeutic applications. Research directed toward these goals often involves administering brain stimulation to healthy normal humans and measuring the effects on cognition. Hence many studies provide an indication of the potential of noninvasive brain stimulation for cognitive enhancement. Both TMS and tDCS have been used with healthy volunteers to induce transient or more lasting improvement in a variety of cognitive domains. Hamilton et al.⁴⁶ have reviewed the empirical literature on cognitive enhancement with noninvasive brain stimulation and, along with Cohen Kadosh et al.,⁴⁷ have discussed the ethical implications of this practice. There are numerous reports of enhanced learning, working memory and other executive functions following TMS or tDCS stimulation, particularly when activating left frontal regions. Enduring enhancement of simple mathematical thinking processes have been achieved by tDCS and tRNS of parietal cortex.^{48,49} There are also reports that creative problem solving can be enhanced with noninvasive brain stimulation, in one case quite spectacularly.⁵⁰

Despite the great promise shown by noninvasive brain stimulation methods so far, we hesitate to draw firm conclusions about the potential of these techniques for cognitive enhancement. The research literature on stimulant medications seemed initially to support their potential as cognitive enhancers. The current state of the brain stimulation literature gives reason for optimism but does not definitively settle the issue of whether these techniques will be helpful for normal healthy individuals seeking to improve their cognitive abilities. In the coming years, replications

and extensions of earlier findings will deliver the evidence that we currently lack (see Ref 51).

The most significant safety risk associated with TMS is the possibility of causing a seizure. However, when administered within the established safety guidelines, the risk of seizure induction is extremely low.⁵² The safety profile of tDCS is even better than that of TMS. Side effects of acute tDCS include sensations such as tingling, burning or pain, rarely experienced as severe⁵³ and no serious adverse health events have ever been reported using this technology.

General Conclusions Regarding Effectiveness of Current Cognitive Enhancement Methods

Given the small size of most of the relevant studies (typically samples of just a few dozen subjects or fewer, limiting the sensitivity of the research), and the likelihood of publication bias against null results, it is difficult to draw definite conclusions concerning the cognitive enhancing effects of either the drugs or stimulation methods discussed here. While the number of positive results makes it seem likely that cognition can indeed be enhanced in the laboratory with drugs and with noninvasive brain stimulation—an implausibly large number of unpublished null or reverse effects would have to exist to attribute all enhancement effects to publication bias—it is difficult to know the true size and generality of these effects at present.

In addition, no studies have yet assessed the carryover from effects on laboratory tests of cognition to effects real-world academic and occupational performance with normal healthy subjects. On the one hand, small effects might only show themselves in the carefully controlled context of laboratory study. Such effects might become imperceptible in real-world work situations. On the other hand, an effect that is small when measured in a single experimental session in the lab may compound itself in ongoing work situations and ultimately yield substantial benefits for the enhancement user. Without the necessary empirical research it is impossible to know how the cognitive enhancers reviewed here might impact real-world users.

EVIDENCE ON PREVALENCE

It is not easy to estimate the prevalence of cognitive enhancement. People are generally reluctant to admit using prescription medications for nonmedical reasons, and this is especially true of prescription stimulants, which are FDA Schedule II controlled substances. Surveys of prescription stimulant use have not, so far, been able to deliver accurate estimates

of pharmaceutical cognitive enhancement in the population at large, and to our knowledge no one has attempted a systematic survey in connection with brain stimulation. Whether involving drugs or devices, the prevalence of cognitive enhancement will undoubtedly differ sharply according to age, gender, occupation, geographic region and other demographic variables, complicating the task of assessing prevalence.

Notwithstanding these limitations, it is possible to draw some inferences from the available evidence, if only for specific segments of the population. Two journals, *Nature* and *Wired*, queried readers about their use of pharmaceutical cognitive enhancement. Although the survey samples were idiosyncratic—people who read the journals and had sufficient interest in the topic of cognitive enhancement to respond—the results can be viewed as a kind of existence proof that cognitive enhancement is being attempted by some. *Nature's* survey was reported in statistical terms, including a 20% rate of self-reported cognitive enhancement among respondents.⁵⁴ *Wired* then asked readers to write in to share their cognitive enhancing regimens, and received 50 reports of 'scientists, college students and business owners' using all of the drugs discussed earlier.⁵⁵

Academic researchers have examined the prevalence of cognitive enhancement with prescription stimulants among students and found widely varying rates of use. Research with various campus samples of convenience in the US have yielded rates of between 2.5 and 55% (see Ref 35 for a review), depending on the nature of the sample and specific wording of the question (e.g., lifetime use versus past month use). The largest and best-designed survey of prescription stimulant use by American undergraduates was undertaken with a representative sample of 10,904 students from 119 different colleges and universities in 2001.⁵⁶ It estimated that, among American college students, 6.9% had used prescription stimulants nonmedically in their lifetime and 4.1% had done so in the past year. It also found large differences between the prevalence of this practice in different parts of the US, at different categories of schools, and among different types of students. The highest rates were found at competitive, Northeastern institutions, among sorority/fraternity members, more likely male and with grade point averages of B or lower. Unfortunately, like the larger national surveys of illicit drug use in the US (the National Survey on Drug Use and Health and Monitoring the Future), this survey did not distinguish between nonmedical use as a study aid and as a recreational drug. This group did carry out a large survey of undergraduates at a

single university and found that the most commonly mentioned reasons for nonmedical stimulant use were to enhance concentration and alertness, but that a substantial number of students also sought the drugs' 'high,'⁵⁷ a finding consistent with many smaller studies at diverse institutions (see Ref 35 for a review).

Little is known about global patterns of cognitive enhancement. It seems that North American students are more likely to use prescription stimulants for enhancement than students from several other countries surveyed, although the small convenience samples used in most of these studies precludes firm conclusions.^{58–60}

To our knowledge there is no systematic research on the use of noninvasive brain stimulation for nonmedical reasons including cognitive enhancement. However, media coverage suggests that the idea has captured the attention and imagination of the public (e.g., Refs 61, 62). The notion that a 'thinking cap' can improve normal performance has been spurred by the advent of tDCS as a therapeutic and investigational tool.

Although TMS has been used in research and clinical settings for over 25 years, the practical limitations of magnetic brain stimulation have largely curtailed interest in its use in normal individuals. TMS units are cumbersome and expensive, require technical expertise to operate, are associated with at least some medical risk, and are generally only available in laboratories or clinical settings. By contrast, tDCS is inexpensive, portable, easy to administer, and apparently safe—properties that are conducive to popular usage. Moreover, the construction of a basic tDCS device is relatively straightforward from an engineering standpoint and can be done inexpensively using readily available materials. This has led a few aspiring entrepreneurs and 'do-it-yourself' enthusiasts to construct tDCS units that are available for purchase by the public (e.g., <http://flowstateengaged.com>, <http://www.foc.us/>). Although it is not possible to

quantify the number of people employing tDCS or other forms of noninvasive brain stimulation outside of research and medicine, an examination of publically accessible websites, blogs, and other social media has turned up a number of intrepid individuals already engaged in self-stimulation for the purposes of cognitive enhancement.

CONCLUSIONS: ISSUES IN NEED OF FURTHER RESEARCH

There are surprisingly few generalizations about cognitive enhancement that can be stated with confidence at present. Published research demonstrates that medications and noninvasive brain stimulation can enhance certain cognitive abilities in normal healthy individuals, although the robustness of these effects—their true size, replicability, and generalizability to nonlaboratory conditions—is unknown. Also poorly understood at present are the possible negative consequences of these practices, from paradoxical impairment of performance in some to the potential for dependency and addiction.

At the same time, we know that some people are sufficiently convinced of the benefits of cognitive enhancement that they have become regular users. We have a sense of the scope of prescription stimulant use for cognitive enhancement in academia, but little beyond anecdotes and existence proofs where other populations and practices are concerned. Given the public health implications of potentially large numbers of healthy people using drugs and devices without medical supervision, we believe that a better understanding of the effects, side effects and prevalence of these methods is a research priority.

NOTES

^a The term is sometimes also used in connection with treatments for cognitive disorders such as dementia.

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