Cognitive enhancement: Can science and policy catch up with practice?

Martha J. Farah

"Man is not going to wait passively for millions of years before evolution offers him a better brain." These words are attributed to the 20th Century Romanian psychopharmacologist Corneliu Giurgea, an early advocate of cognitive enhancement – that is, the use of medications for improving normal healthy cognition. Contemporary attempts at cognitive enhancement involve an array of drugs and devices for modifying brain function, from pills taken by students to help them study to electrical stimulators focused on prefrontal cortex by e-gamers to sharpen their skills. What do we know about current methods of cognitive enhancement? What specifically do they enhance, for whom, and with what risks? We know surprisingly little.

We do know that stimulants such as amphetamine and methylphenidate (sold under trade names such as Adderall and Ritalin, respectively) are widely used for nonmedical reasons by Americans (1). However, it is not known how many of these users are seeking cognitive enhancement, as opposed to getting high, losing weight or some other effect. Student surveys suggest that cognitive enhancement with stimulants is commonplace on college campuses, where students with prescriptions sell surplus pills to other students, who use them to help study and finish papers and projects (2). Similar use by college faculty and other professionals has been documented but prevalence is unknown (eg 3, 4).

These practices have been interpreted as paradigm cases of cognitive enhancement, generally aimed at improving executive function (EF), the ability to marshal cognitive resources for flexible multitasking or focusing, as needed. Because these drugs are widely used to treat Attention Deficit Hyperactivity Disorder (ADHD), in which EF is impaired, they are assumed to enhance EF in healthy individuals as well. However, the current evidence suggests a more complex state of affairs. The published literature includes substantially different estimates of the effectiveness of prescription stimulants as cognitive enhancers. A recent meta-analysis suggests that the effect is most likely real but small for EF tests stressing inhibitory control, and probably nonexistent for EF tests stressing working memory (5).

Why, then, do these drugs continue to be used for enhancement? One possibility is that there are important individual differences in people's response to them, with some people benefitting (2). In addition, stimulants have other effects for which they may be used. In a report entitled "Just How Cognitive is 'Cognitive Enhancement'?" sociologist Scott Vrecko interviewed students who used Adderall and found that they emphasized motivational and mood effects as reasons for using the drugs for schoolwork (6). Subsequent research confirmed the role of these noncognitive factors for students enhancing with Adderall; while they differed minimally from nonusers on attention task performance, they exhibited greater differences in motivation and worse study habits, along with more depressed mood (7).

There is, of course, a close relation between cognitive performance, on the one hand, and motivation, on the other. Even if one's laboratory-measured EF is not appreciably increased, one is likely to get more done, of better quality, if one is feeling cheerful and "into" the tasks at hand. Unfortunately, the mood- and motivation-boosting abilities of stimulants are related to their well-known dependence potential, and that potential is a significant safety concern. How likely is cognitive enhancement use of stimulants to lead to dependence? The prevalence of drug dependence among enhancement users is not currently known.

Another drug used for cognitive enhancement is modafinil (trade name Provigil). Best known for its ability to preserve alertness and cognitive function under conditions of sleep deprivation, it may also enhance aspects of cognition in rested individuals. As with amphetamine, studies have produced conflicting results. A recent literature review of the cognitive effects of modafinil found enhancement, null effects and occasionally impairment. Enhancement was the most common finding, especially in complex cognitive tasks, although effect sizes were not synthesized through meta-analysis to yield a quantitative summary measure of effectiveness (8). A recent article, reporting a "striking increase in task motivation," suggested that this may contribute to modafinil's value as a cognitive enhancer in the workplace (9), although motivational effects are inconsistent across studies (8). Modafinil's dependence potential is believed to be low, although some would not discount the risk (10).

The newest trend in cognitive enhancement is the use of transcranial electric stimulation (tES; 11. In the most widely used form of tES, transcranial direct current stimulation (tDCS), a weak current flows between an anode and a cathode placed on the head, altering the resting potential of neurons in the current's path. The simplicity and low cost of tDCS devices have enabled wide use of the technology for research and, increasingly, for home use. No epidemiological data exist on the use of these devices, but the internet abounds with discussion and advice on how to build and use tDCS systems. An initial survey with a convenience sample recruited from internet sites indicates that cognitive enhancement is the most common reason for personal use of tDCS (12). Subscribers to the main tDCS interest website number in the thousands (12), but actual prevalence and related information about tDCS use is unknown.

The true cognitive benefit of tDCS in normal healthy users is also unknown. As with research on pharmaceutical enhancement, the published literature includes a mix of findings. One recent attempt to synthesize the literature with meta-analysis concluded that tDCS has no effect whatsoever on a wide range of cognitive abilities (13). However, the methods of this analysis have been criticized as unnecessarily conservative and even biased (14). Newer tES protocols, involving alternating current stimulation (tACS), random noise stimulation (tRNS) and pulsed stimulation (tPCS), have different physiological effects and hence potentially different psychological effects, although the empirical literature is still developing.

TES is expanding beyond home hobbyists, with new companies selling compact, visually appealing, user-friendly devices. These have been exempted from regulation as medical devices by the US FDA. Foc.us markets its systems to gamers to improve attention and performance. Thync, which began selling its system in June of this year, is intended for a much broader set of lifestyle uses, comparable to coffee for work and meditation for relaxation. At present there is little scientific evidence for or against the effectiveness of these specific systems, nor is there evidence concerning physiological and psychological effects of regular use over months or years in humans or in animals.

To summarize the state of empirical knowledge regarding cognitive enhancement, it remains difficult to say what cognitive benefits these practices offer, in the lab let alone in the classroom or workplace, and attendant risks are even harder to gauge. While surveys have estimated the number of college students using stimulants for enhancement, little is known about other people and other practices. Without knowing more about the prevalence, risks and benefits of these brain interventions, it is difficult to formulate useful policy.

Why are we so ignorant? Several factors seem to be at play. The majority of studies of enhancement effectiveness have been carried out on small samples, rarely more than 50 subjects, which limits their power. Furthermore, cognitive tasks typically lend themselves to a variety of different but reasonable outcome measures, such as overall errors, specific types of errors (eg, false alarms) and response times. In addition there is usually more than one possible statistical approach to analyzing the enhancement effect. Small samples and flexibility in design and analysis raise the likelihood of published false positives (15). In addition, pharmacologic and electric enhancements may differ in effectiveness depending on the biological and psychological traits of the user, which complicates the effort to understand the true enhancement potential of these technologies. Industry is understandably unmotivated to take on the expense of appropriate large-scale trials of enhancement, given that the stimulants used are illegally diverted and tES devices can be sold without such evidence. The inferential step from laboratory effect to real world benefit adds another layer of challenge. Finally, given that enhancements would likely be used for years, long-term effectiveness and safety are essential concerns but are particularly difficult and costly to determine. As a result, the only large-scale trial we may see is the enormous but uncontrolled and poorly monitored trial of people using these drugs and devices on their own.

1. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. *NSDUH* Series H-48, HHS. Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration.

2. Smith, M. E., & Farah, M. J. (2011). Are prescription stimulants “smart pills”? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological bulletin*, *137*(5), 717.

3. Maher, B. (2008). Poll results: look who's doping. *Nature*, *452*, 674-675.

4. Schwarz, A. (2015). Workers Seeking Productivity in a Pill Are Abusing A.D.H.D. Drugs. *New York Times*, April 18.

5. Ilieva, I. P., Hook, C. J., & Farah, M. J. (2015). Prescription Stimulants' Effects on Healthy Inhibitory Control, Working Memory, and Episodic Memory: A Meta-analysis. *Journal of cognitive neuroscience*.

6. Vrecko, S. (2013). Just how cognitive is “cognitive enhancement”? On the significance of emotions in university students’ experiences with study drugs. *AJOB neuroscience*, *4*(1), 4-12.

7. Ilieva, I. P., & Farah, M. J. (2015). Attention, motivation, and study habits in users of unprescribed ADHD medication. *Journal of attention disorders*, 1087054715591849.

8. Battleday, R. M., & Brem, A. K. (2015). Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: a systematic review. *European Neuropsychopharmacology*.

9. Müller, U., Rowe, J. B., Rittman, T., Lewis, C., Robbins, T. W., & Sahakian, B. J. (2013). Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology*, *64*, 490-495.

10. Volkow, N. D., Fowler, J. S., Logan, J., Alexoff, D., Zhu, W., Telang, F., ... & Apelskog-Torres, K. (2009). Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *Jama*, *301*(11), 1148-1154.

11. Dubljević, V., Saigle, V., & Racine, E. (2014). The rising tide of tDCS in the media and academic literature. *Neuron*, *82*(4), 731-736.

12. Jwa, A. (2015). Early adopters of the magical thinking cap: a study on do-it-yourself (DIY) transcranial direct current stimulation (tDCS) user community. *Journal of Law and the Biosciences*, lsv017.

13. Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain stimulation*.

14. Price, A. R., & Hamilton, R. H. (2015). A Re-evaluation of the Cognitive Effects From Single-session Transcranial Direct Current Stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*.

15. Ioannidis JPA (2005) Why most published research findings are false. *PLoS Med* 2: e124. doi: 10.1371/journal.pmed.0020124.