crystal momentum space. This, however, is not important, as a similar effect should be observed in Weyl semimetals, where opposite-chirality fermions exist at distinct points in momentum space. The way that the chiral anomaly manifests in Na_3Bi is through magnetoresistance (a dependence of the electrical resistance of the material on an applied magnetic field). The physical picture of the chiral anomaly, when applied to a Dirac or Weyl semimetal, implies a magnetic field–dependent contribution to the resistance, which is negative (the resistance is reduced and the material becomes a better conductor when the magnetic field is applied) and quadratic in the field (*10*, *11*). The effect also exists only when the current is aligned with the direction of the field (the magnetoresistance is longitudinal), survives up to a temperature of about 90 K, and is large (quickly rising to more than 100% as the temperature decreases below 90 K). These features are unusual and cannot be explained by any other known mechanism but the chiral anomaly.

What makes the observed effect important, apart from the analogy to particle physics, is that the chiral anomaly is a purely quantum mechanical phenomenon without any classical analogs. Yet the observed longitudinal magnetoresistance is a macroscopic effect, seen in a large sample. Such macroscopic quantum phenomena are typically observed only at very low temperatures. The fact that the chiral anomaly manifestation in Na_3Bi is observed at temperatures as high as 90 K makes it especially interesting and potentially useful technologically. ■

"...the chiral anomaly is a purely quantum mechanical phenomenon without any classical analogs. Yet the observed longitudinal magnetoresistance is a macroscopic effect..."

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NEUROSCIENCE

The unknowns of cognitive enhancement

Can science and policy catch up with practice?

By **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 or other brain treatments for improving normal healthy cognition. Contemporary attempts at cognitive enhancement involve an array of drugs and devices for modifying brain function, such as pills taken by students to help them study, or electrical stimulators focused on prefrontal cortex by electronic game players ("e-gamers") to sharpen their skills. What is known about current methods of cognitive enhancement? What specifically do they enhance, for whom, and with what risks? We know surprisingly little.

In the United States, stimulants such as amphetamine and methylphenidate (sold under trade names such as Adderall and Ritalin, respectively) are widely used for nonmedical reasons (*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—there is simply a lack of epidemiological data. Student surveys suggest that cognitive enhancement with stimulants is commonplace on college campuses, where students with prescriptions sell pills to other students, who use them to help study and finish papers and projects (*2*). Similar use by college faculty and other professionals to enhance workplace productivity has been documented, but prevalence is unknown (*3*, *4*).

These practices have been interpreted as paradigm cases of cognitive enhancement (which is distinct from treatment for a cognitive disorder) generally aimed at improving executive function—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 executive function is impaired, they are assumed to enhance executive function 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 executive function tests stressing inhibitory control, and probably nonexistent for executive function 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 benefiting (*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; although they differed minimally from nonusers on attention task performance, they exhibited substantially 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 executive function is not appreciably increased, one is likely to get more done, and 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 major concern. How likely is it that cognitive enhancement use of stimulants will 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

Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104, USA. E-mail: mfarah@psych.upenn.edu

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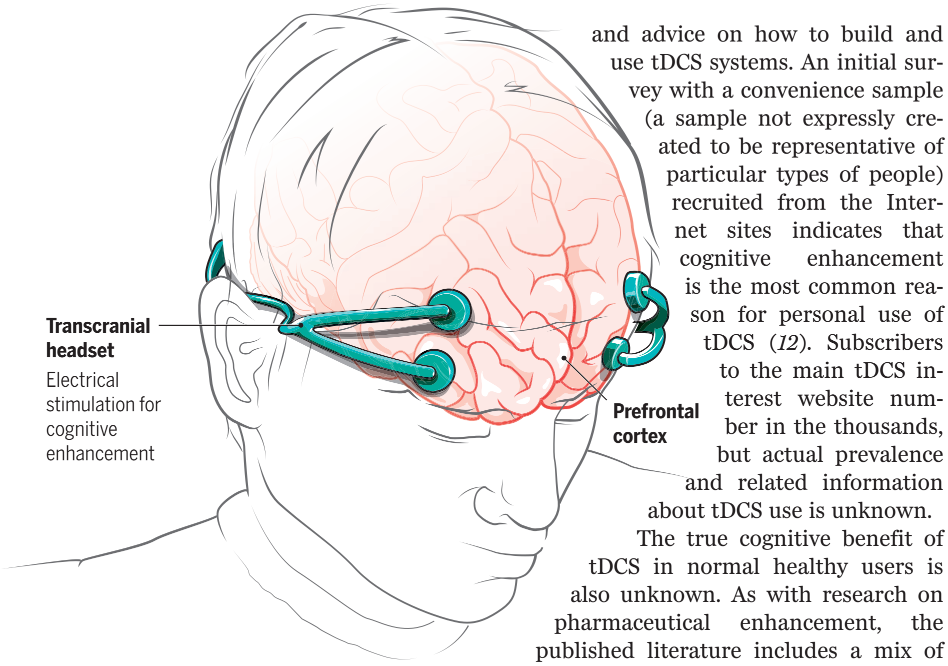

New trends. Transcranial electric stimulation for cognitive enhancement in healthy individuals is becoming more popular, yet little is known about the effectiveness or long-term safety of these devices.

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 a range of outcomes: enhancement, null effects, and occasionally impairment. Enhancement was the most common finding, especially in complex cognitive tasks requiring multiple components of executive function to be used together, although effect sizes were not synthesized through meta-analysis to yield a quantitative summary measure of effectiveness (*8*). A recent study reported a "striking increase in task motivation," suggesting that this may contribute to modafinil's value as a cognitive enhancer in the workplace (*9*), but 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 (*11*). In the most widely used form, called 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 broad 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 (a sample not expressly created to be representative of particular types of people) recruited from the 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, 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 transcranial electric stimulation 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.

Transcranial electric stimulation is expanding beyond home users, with new companies selling compact, visually appealing, user-friendly devices. These have been exempted from regulation as medical devices by the U.S. Food and Drug Administration. One company, Foc.us, markets its systems to e-gamers to improve attention and performance. Thync, which began selling its system in June of this year, targets a broader set of lifestyle uses, comparable to coffee for work and meditation for relaxation. At present, there is little to no scientific evidence for or against the effectiveness of these specific systems, nor is there evidence concerning the physiological and psychological effects of regular use over months or years in humans or in animals.

It remains difficult to say what cognitive benefits these various practices offer in the laboratory, let alone in the classroom or workplace, and their attendant risks are even harder to gauge. Although 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 about cognitive enhancement? Several factors seem to be at play. The majority of studies on 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 (for example, false alarms), and response times. In addition, there is usually more than one possible statistical approach to analyze 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 transcranial electric stimulation devices can be sold without such evidence. The inferential step from laboratory effect to real-world benefit adds another layer of challenge. 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. ■

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