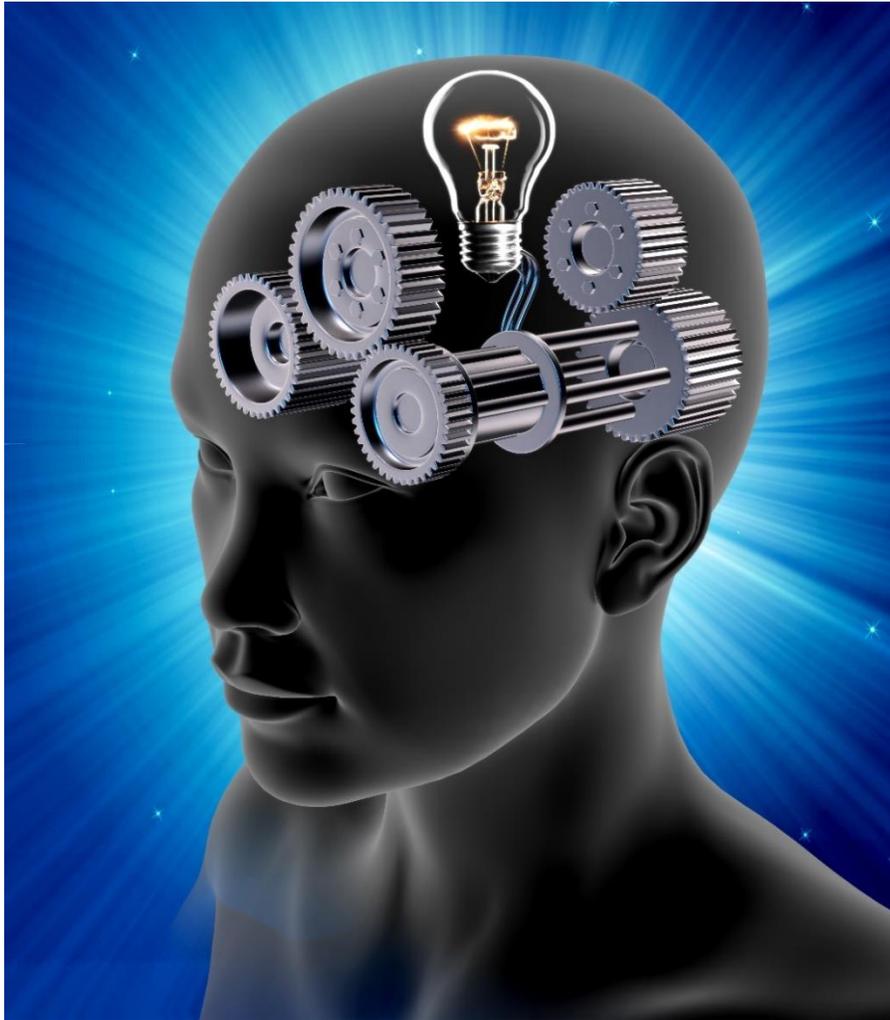


## The Illusion of the Perfect Brain Enhancer

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*Editor's Note: Many questions loom over transcranial direct current stimulation (tDCS), a non-invasive form of neurostimulation in which constant, low current is delivered directly to areas of the brain using small electrodes. It was first established in neuroscience research in the 1950s and 60s, but has seen rapid growth, particularly in the last five years. Originally developed to help patients with brain injuries such as strokes, tDCS is now also used to enhance language and mathematical ability, attention span, problem solving, memory, coordination, and even gaming skills. The authors examine its potential and pitfalls.*

**W**ho doesn't want to get smarter? Who doesn't want to improve their grades, make better decisions, perform at work with greater success, be more skillful at a sport, or just excel at playing videogames?

Of course, there are ways to pursue such goals, but they require significant time, effort, dedication, and practice with no assurance of results. Any skill, from the simple ability to grab a cup of coffee to the complex challenge of piloting a fighter jet, depends on an intricate net of brain connections, shaped over many years of learning and consolidation processes. (The Spanish neuroscientist and Nobel Prize winner, Santiago Ramón y Cajal, was the first to make this point based on his notions about neuroplasticity, the brain's capacity to change and adapt.)

But our society has made us impatient, entitled, and unwilling to sacrifice and work hard. Most of us wish upon a star and hope for a miracle—or, at a minimum, a way to shorten the time and reduce the effort needed. Even if we weren't able to learn faster or more efficiently, perhaps most of us would settle for some help in improving on whatever we are trying to accomplish.

Unfortunately, not everyone is equally talented or fit for every job, sport, or academic career. For some people, it takes much longer than for others to gain a given skill, and many will never get there at all. All brains are not created equal, in other words. Current studies are in fact working to identify differences in brain structures and functions—"brain fingerprints"—that might predict an individual's response to a given intervention and cognitive training protocol, or capacity to acquire a new skill. The emerging appreciation of such differences, along with notions of genetic determinism, make it particularly tempting to seek ways to escape biological constraints, modify one's baseline talents, and become able to acquire capacities one could otherwise only dream of: to play soccer like Lionel Messi or tennis like Roger Federer, run like Usain Bolt, paint like Pablo Picasso, or sing like Luciano Pavarotti.

### **The Two Sides of Brain Stimulation**

Over the last decade, a new class of "brain augmentation" products has entered the market, under the label of transcranial direct current stimulation, or tDCS. This neuromodulatory technique is one of several Non-Invasive Brain Stimulation (NIBS) methods that have been the subject of increasing neurobiological research, and have promising applications for various neuropsychiatric conditions.<sup>12</sup>

But non-medical, largely experimentally untested applications are also being embraced—and raising concern.

tDCS has roots in 200 year-old experiments by Luigi Galvani, a pioneer of bioelectromagnetics, and his nephew, Giovanni Aldini.<sup>3</sup> It is thought to exert its effects through brain polarization: low-voltage electrical currents supposedly induce shifts in the concentration of free floating charged particles in brain tissue, making neurons less or more excitable depending on the polarity of the electrical field.<sup>4</sup> Compared to the complex hardware required for Transcranial Magnetic Stimulation (TMS)<sup>5</sup>—the most established NIBS technique, for which several devices have been cleared by the Food and Drug Administration (FDA) to treat medication-resistant depression—tDCS stimulators are quite simple, the equivalent of a nine-volt battery and a simple electronic circuit connected to two or more surface electrodes.

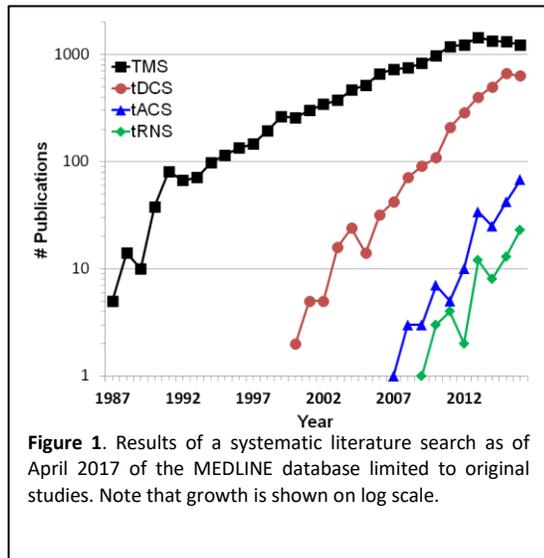
Given the device's low cost, ease of application, and apparent safety across research studies, it is easy to understand why the use of tDCS outside laboratory walls has grown exponentially in the last few years. It has been marketed to increase cognitive abilities, including memory and abstract reasoning, enhance mood and energy, and even improve video-gaming skills and physical performance. Among athletes who reportedly have used tDCS are competitors at the Olympic Games in Brazil<sup>6</sup> and players for the Golden State Warriors of the NBA.<sup>7</sup> Professional video gamers were recently reported to have used tDCS in preparation for a \$1 million competitive event, and online forums and blogs are full of do-it-yourself (DIY) guides for building devices that promise to make you smarter, faster, and more efficient.<sup>8</sup>

Such flamboyant non-medical applications are not without precedent: In 1804, Giovanni Aldini and several followers became celebrities who performed public demonstrations of brain “Faradizing” for entertainment at parties and public events, and boasted it might be even possible to revive the dead with the technique. They, however, lacked such 21<sup>st</sup> century refinements as Bluetooth capabilities that make some portable tDCS devices as ready as everyday gizmos.

Obviously, the reality of tDCS effects and those of similar devices based on different principles (e.g. ultrasound stimulation<sup>9</sup>) is more complicated, and we ought to learn from history and neuroscience, and avoid making mistakes that can be costly for the individual and the progress of knowledge.

## Unique Neuroscience and Clinical Tools

NIBS provides unique tools to understand and modify brain function. These include transcranial magnetic stimulation (TMS), which induces electric current in the brain via powerful, brief magnetic pulses created by a coil held over the subject's head;<sup>10</sup> and variants of transcranial current



stimulation (tCS)—direct or alternating current stimulation (tDCS, tACS) and random noise stimulation (tRNS)—which deliver low-voltage current through surface electrodes attached to the subject's head.<sup>11,12</sup>

Temporally interfering electric stimulation (TI) promises to allow selective stimulation of deep brain structures. Transcranial infrared light stimulation modulates neuronal activity and brain oscillatory activity, while low-intensity focused ultrasound pulsations can induce neuronal excitation and

inhibition without anatomical damage and with exquisite spatial precision, including the ability to selectively target white matter tracts.<sup>13,14</sup>

Such techniques are being adopted in fundamental, translational, and clinical brain research (Figure 1, adapted from<sup>15</sup>), and offer promise as diagnostic and therapeutic interventions for diverse diagnoses, symptoms, and disabilities. The field has been rapidly expanding, spurred partly by advances in computational, electronic, biological, and brain imaging technologies. While deeper understanding of the mechanisms of action of NIBS techniques is needed, studies using them can offer valuable insights into core principles of brain function and brain-behavior interactions. NIBS affects distributed brain networks, and can modulate brain activity in a controlled manner.<sup>16,17</sup> By inducing transient changes in brain activity, it can be deployed to experimentally test psychological and cognitive theoretical models, and to evaluate cause and effect relationships between a behavior (e.g., cognitive process) and activity in specific brain regions.

In the first demonstration of its potential, Pascual-Leone and colleagues used repetitive TMS (rTMS) to transiently induce speech arrest in healthy humans.<sup>18</sup> This work indicated that rTMS and similar brain perturbation approaches could be valuable to study the neurobiological substrates of human

brain disorders, shedding light into the basis of neurological and psychiatric brain dysfunctions through “virtual lesions.”<sup>10</sup>

More broadly, NIBS has offered insights into the neural substrates of mood and emotion,<sup>19</sup> decision making,<sup>20,21</sup> and moral judgement.<sup>22</sup> Combined with brain imaging and neurophysiologic methods, it can be used to characterize spatio-temporal properties of neural networks. Combining TMS with brain imaging makes it possible to examine the effects of a controlled perturbation of specific brain functional networks,<sup>23,24</sup> as was recently done to determine the relationships between behaviors and specific patterns of multi-region activity in the context of associative memory.<sup>25</sup>

Beyond *spatially* distributed neural networks, brain function involves the dynamic, i.e., time-varying, function of networks of brain regions. NIBS methods can offer unique insights into such *temporal* dynamics, including oscillatory mechanisms and patterns. Combined with EEG (an electrophysiological monitoring method to record electrical activity of the brain), they can be used to assess the temporal and spatial connectivity of brain regions in different behavioral and disease states,<sup>26-27</sup> the frequency response of different brain regions to brief stimulation,<sup>28</sup> and the compensatory frequency and connectivity changes that occur with longer-lasting perturbations.<sup>27,29</sup> In addition, NIBS can directly modulate the spatially-localized oscillations involved in complex cognitive functions,<sup>30,31</sup> including those dysregulated in disease states.

Importantly, NIBS approaches are applicable across the lifespan and offer translatable biomarkers to bridge the challenging divide between animal models and human studies. The real-time integration of NIBS with EEG or Magnetic Resonance Imaging (MRI) enables the study of brain effects of the induced perturbation and can provide unique insights into spatial-temporal properties of the system that can be related to cognitive or behavioral abilities, used to classify clinical phenotypes, or serve as biomarkers for genetic explorations. The application of the same methods of assessing brain function in human and animal models offer translational phenotypes to integrate model (animal) systems and human studies.

In addition, there are growing clinical applications of NIBS. Four different systems for TMS have been cleared by the FDA for treatment of medication-resistant depression, and Medicare as well as most health insurance companies now provides coverage for it. A home-based, self-delivery TMS system has been cleared by the FDA for treatment of migraine, and another has been approved for pre-

surgical mapping of motor and language functions. Several companies are conducting pivotal studies aimed at regulatory clearance of TMS and tCS devices for other indications, including schizophrenia, Alzheimer's disease, epilepsy, developmental disabilities such as dyscalculia and autism, and recovery from stroke.

Meanwhile, a growing number of hospital-based clinical programs and private practice clinics have been established, offering TMS and tCS to patients with a range of medical diagnoses, some "on-label" given FDA approval, and others "off-label," on the basis of published evidence but lacking FDA endorsement. Several companies are offering direct-to-consumer NIBS devices and there is a rapidly growing movement of Do-It-Yourself (DIY) adopters. However, fundamental questions remain, emphasizing the need for well-trained scientists conducting rigorous, high-quality studies on the mechanisms of action of NIBS modalities, properly powered studies on their therapeutic efficacy, and careful evaluation of potential risks, complications, and adverse effects.

### **Beyond Neuroscience and Clinical Medicine**

In the case of tDCS, since its re-discovery by two independent teams of scientists in Italy and Germany<sup>12,32</sup> around two decades ago, this modality has been increasingly adopted in clinical and experimental settings.<sup>15</sup> Evidence-based clinical efficacy in large clinical trials is still moderate to weak, but studies show some value for almost any neurological and psychiatric disorder that has been tested, both in combination with other treatments (e.g., psychotherapy for depression and anxiety, cognitive remediation for schizophrenia, physical therapy for stroke) or as a stand-alone intervention.

As to enhancement of normal cognitive function, tDCS—as well as tACS and tRNS—have been used in attempts to amplify basically any domain, from attention to perception, language acquisition to working memory, visuo-motor coordination to intelligence. Although findings in these areas have often been presented in the context of underpowered, poorly controlled studies,<sup>15</sup> meta-analysis of available data (for an example see <sup>33</sup>) seem to support the efficacy of tDCS in different cognitive domains, but suffer from the likelihood of publication bias in the primary studies. Certainly, increasing knowledge about individual differences in the response to stimulation, the role of genetic determinants, and potential long-term (positive and negative) effects on brain function, suggest that we may just be observing the tip of the tDCS research iceberg.

Outside laboratory walls, there are more than a dozen companies marketing devices for brain stimulation, ranging from DIY kits for assembling a basic device at home, to high-end products like the “Halo” brain stimulation headphones, advertised as a \$700 professional aide for elite athletes.<sup>34</sup> Detailed guidelines on how to build a tDCS device using \$20 worth of electronic components are easy to find online, and a Reddit forum on tDCS which opened in 2013,<sup>35</sup> reports around 10,000 visitors per month. What might have constituted an underground culture has grown at an unexpected rate, leading to warning messages by the scientific community.<sup>36,37</sup> At issue are clearly not just the risks of DIY stimulation, but also its ethical regulation, with experts suggesting the need of new bioethical models.<sup>38,39–41</sup> Before addressing this knotty issue, it is important to understand what is actually at stake when we start “playing” with the brain.

### **Beware of Complexity**

A tDCS device may be easy to build and the stimulation may be simple to apply, but its effects on the brain are far from straightforward. They represent the interaction between the applied current and the targeted brain area’s structure and function, and it is worth remembering that the brain is the most complex network known to humans.<sup>42</sup> Can the application of a weak electric field for around 20 minutes at an almost imperceptible intensity operate in a controlled, safe, predictable manner, only inducing beneficial effects? When things seem too good to be true, they are generally false.

In a recent open letter to the tDCS DIY community published in *Annals of Neurology*,<sup>37</sup> Wurzman and colleagues pointed out a number of issues surrounding such use: that the parts of brain stimulated by tDCS and effects induced are less deterministic than one may think; that functional gains may be associated with meaningful tradeoffs; and that tDCS-induced brain changes may be long-lasting and could lead to enduring complications and deleterious effects as yet unknown. Before engaging in DIY brain stimulation, it seems critical to be aware of many of the unanswered questions about the mechanisms of action and effects of tDCS.

Among these areas of uncertainty: first, even though one may aim to target a given brain region, the effects of tDCS are never limited to the area between the electrodes. Current flows in complex ways, depending on which tissues it encounters, can affect the function of structures along its path. In addition, stimulation affecting activity in one region will always modulate activity in others because

the brain is organized in intricate networks of interconnected regions. Through such widespread effects, tDCS may alter brain functions in unintended ways.

Second, selectively influencing a given brain function with tDCS is challenging. For instance, the main target of studies using tDCS to increase working-memory, attention, abstract reasoning, and mood has been the dorsolateral prefrontal cortex (DLPFC), which is highly interconnected with much of the brain, including cortical, subcortical, and brainstem regions. Presumably, tCS effects can spread across these diverse networks inducing behavioral and cognitive effects that will not be monitored during such experiments. In this context, it is also important to note that tCS interacts with ongoing brain activity and can have a different effect on neurons that are active during stimulation compared to those that are not. Thus, the specifics of brain activity, including the expectations of cognitive or behavioral consequences, can modify tCS effects. Stimulation while one is reading a book, meditating, visually fixating on a crosshair, watching TV, doing arithmetic, sleeping, or playing video games could all cause different changes in one's brain circuitry. In fact, even activity before tCS is applied may change its impact. At this point, we do not know how much such variables can influence the effect of tCS, or what is the best activity to achieve a certain change in brain function or behavioral impact.

Third, because of the complex organization of the brain and its dynamically interacting networks, modifying activity in one network with tCS can change the activity in others in a way that we cannot reliably predict: enhancement of some cognitive abilities may come at the cost of others. tCS may, for example, improve the ability to perform a task dependent on a given brain network, but hurt another because of interactions between networks.<sup>43</sup> It is important to note that such potential tradeoffs are generally under-recognized, as most studies focus on just one or two tasks, and deleterious effects may develop over time and only become recognizable long after the stimulation.

Fourth, changes in brain activity resulting from tCS, whether intended or unintended, may last longer than anticipated. Because of processes of brain plasticity, tCS may initiate a cascade of phenomena that could lead to enduring and even self-perpetuating brain changes. Studies suggest that cognitive enhancements (as well as concurrent tradeoffs) may persist for over six months after stimulation.<sup>44</sup> Ongoing, regular application of tCS may effectively sustain desired effects, but also increase risks of lasting undesirable consequences. Furthermore, the possible risks of a cumulative dose over years or a lifetime have not been sufficiently studied. Put bluntly, we simply do not know what potential long-term consequences tCS may have.

Finally, it is critical to remember that each of us is different and that the effects of tCS vary greatly across individuals: the impact of 20 minutes of tCS at a given intensity on the brain of a 65-year-old former accountant is very likely not the same as on the brain of a 16-year-old high-school student. Reading the scientific literature with an untrained eye might lead to cherry-picking data in favor of the expected outcome, while neglecting the fact that, for example, up to 30 percent of experimental subjects may respond to the identical tCS setting with cortical excitability changes in the opposite direction from most subjects.

The results reported in scientific papers are averages across participants, but frequently fail to address the high individual variability in response to stimulation.<sup>45</sup> Most importantly, even under controlled experimental conditions when a consistent modulatory effect is achieved in all the subjects, variance in the magnitude of the behavioral effects at the individual level is still high,<sup>46</sup> possibly leading to unpredictable and potentially detrimental consequences.<sup>47</sup> Such variability is clearly not monitored by the DIY community, and the same often applies to the scientific literature, in which negative findings are less consistently reported and shared on the Web. To complicate things further, gender, age, neuroanatomy, spontaneous brain activity patterns, hormones, genetic polymorphisms, and even prior exposure to brain stimulation can all potentially affect the result of a tCS session.<sup>46</sup>

Despite the above uncertainties and risks, numerous scientific studies apply repeated sessions of tCS with the intent of causing lasting changes in brain function. They are, however, almost always performed in patients with neurological or psychiatric brain diseases with the goal of alleviating symptoms, in clinical trials that are carefully designed and regulated, provide detailed disclosure of risks, and obtain informed consent of participants. Application of tCS to healthy subjects poses very different risk-benefit considerations. To complicate matters, many direct-to-consumer devices leave decisions as to stimulation timing, intensity, and duration up to users who may, in some cases, apply it multiple times per day for many months while doing different things. It is important to consider that because the impact of such long courses of repeated sessions of tCS have not been assessed, even in laboratory settings, users are truly unable to assess the risks to which they may be exposing themselves in the pursuit of cognitive enhancement.

### **The Right to Do It Wrong**

Despite all open questions and uncertainty of risk, the most fundamental consideration might be whether we should be free, if we so choose, to subject our brains to whatever type of electrical stimulation we like. We would answer “yes,” but it is a complex issue.<sup>38,48</sup> Are we facing a new type of “doping” which might require ad-hoc regulations, at least for its use in professional sport contexts? Is there enough evidence of risk to constitute a serious issue for the lay public, requiring some sort of medical monitoring when tCS is performed in any setting?

Perhaps, the response to these questions is “coffee.” Even though coffee companies do not advertise that the effect of a shot of espresso has the spatial accuracy of tCS targeted to one specific brain region, the effects of coffee on cognitive functioning are indisputable.<sup>49</sup> So, why not regulate coffee intake? We also know that some studies found excessive coffee intake might be detrimental for general health,<sup>50</sup> but agree that self-regulation of coffee consumption is acceptable. On the other hand, one might say that if different types of coffee with selective effects on memory, attention, and logical reasoning were available, the same principle would no longer apply and we would have to discuss whether athletes should be allowed to take the espresso affecting reaction times while being free to take the memory-enhancing one.

So, is the difference simply that coffee’s generalized, non-specific effect on brain activity makes it acceptable, while the specificity of tCS (it can—theoretically—target a given brain region, and directly affect brain physiology and associated cognitive function), represents “doping?” A lot of things affect brain physiology: talking with a friend about your troubles might make you change your mind about what to do tomorrow morning, because a series of chemical reactions in the brain strengthen and weaken different sets of connections, allowing a new thought to emerge to consciousness. The same applies when learning a new language or solving a puzzle.

The question is how long the same processes might take if induced by “natural” means (e.g., a conversation or 100 hours spent on a language-acquisition app on the smartphone) or if facilitated by making brain plasticity and learning processes more efficient through brain stimulation.

Any advancement that might help achieve a personal goal in the context of a fair competition (e.g., where everyone has access to and can use tCS) should be allowed, as everyone is permitted to use the latest cutting-edge swimsuit, the best vitamin supplement to recover after a soccer training session, or the lightest carbon-fiber bicycle on the market. The ethical principles of autonomy,

equality, justice, and universalism apply. However, utilitarianism is a real issue because of the gaps in our knowledge of the potential consequences of long term use of tCS. It might well be worth asking what could be lost in the long term, rather than simply what might be gained in the short one.

### Bios

**Emiliano Santarnecchi**, Ph.D., is an instructor of neurology and co-director of the CME course in Transcranial Current Stimulation (tCS) at Harvard Medical School and a clinical research scientist at the Berenson-Allen Center for Non-invasive Brain Stimulation at the Beth Israel Medical Deaconess Center. His research involves Non-Invasive Brain Stimulation (NIBS), electrophysiology, and neuroimaging methods. He is currently testing the application of transcranial alternating current stimulation (tACS) to induce long-lasting changes in brain oscillations, which might translate into therapeutic options for patients with Alzheimer's disease. Santarnecchi obtained his Ph.D. in applied neurological sciences at the University of Siena School of Medicine in Italy.

**Alvaro Pascual-Leone**, M.D., Ph.D., is professor of neurology and an associate dean for clinical and translational research at Harvard Medical School. He is chief for the Division of Cognitive Neurology and the director of the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center. Pascual-Leone is a practicing cognitive neurologist and researches the mechanisms that control brain plasticity across the life span. He is considered a world leader in the field of noninvasive brain stimulation, where his contributions span from technology development through basic neurobiologic insights from animal studies and modeling approaches, to human proof-of-principle and multicenter clinical trials. Pascual-Leone obtained an M.D. and a Ph.D. in neurophysiology in 1984 and 1985 respectively, both from the Faculty of Medicine of Freiburg University in Germany. He also trained at the University of Minnesota, the US National Institutes of Health, and the Cajal Institute of the Spanish Research Council.

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