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Mechanisms and Effects of Transcranial Direct Current Stimulation

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Abstract

The US Air Force Office of Scientific Research convened a meeting of researchers in the fields of neuroscience, psychology, engineering, and medicine to discuss most pressing issues facing ongoing research in the field of transcranial direct current stimulation (tDCS) and related techniques. In this study, we present opinions prepared by participants of the meeting, focusing on the most promising areas of research, immediate and future goals for the field, and the potential for hormesis theory to inform tDCS research. Scientific, medical, and ethical considerations support the ongoing testing of tDCS in healthy and clinical populations, provided best protocols are used to maximize safety. Notwithstanding the need for ongoing research, promising applications include enhancing vigilance/attention in healthy volunteers, which can accelerate training and support learning. Commonly, tDCS is used as an adjunct to training/rehabilitation tasks with the goal of leftward shift in the learning/treatment effect curves. Although trials are encouraging, elucidating the basic mechanisms of tDCS will accelerate validation and adoption. To this end, biomarkers (eg, clinical neuroimaging and findings from animal models) can support hypotheses linking neurobiological mechanisms and behavioral effects. Dosage can be optimized using computational models of current flow and understanding dose–response. Both biomarkers and dosimetry should guide individualized interventions with the goal of reducing variability. Insights from other applied energy domains, including ionizing radiation, transcranial magnetic stimulation, and low-level laser (light) therapy, can be prudently leveraged.

Keywords

tDCS, hormesis, hormetic, dose–response, biphasic, electrical stimulation

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Introduction and Background: Brain Stimulation and Hormesis (Walter J. Kozumbo)

For a number of years, the US Air Force Office of Scientific Research (AFOSR) has supported research to elucidate and engage brain mechanisms that can fortify health and performance. Consistent with the recently announced *Brain Research through Advancing Innovative Neurotechnologies* initiative, current efforts have focused upon the development, use, and assessment of interventional tools and techniques that harness cutting-edge approaches in bioengineering in synergy with the biological, chemical, physical, and cognitive sciences. Fundamental to this approach is the need for defined outcomes and an iteratively more detailed understanding of the mechanisms inherent in these novel approaches.

Current iterations of neurotechnology, including neuromodulatory techniques such as transcranial direct current stimulation (tDCS), show considerable potential as stand-alone modalities for treating neuropsychiatric disorders and improving neurocognitive performance. In addition, many of these techniques can be used in place of or in tandem with other interventions, including pharmacologic agents, cognitive and behavioral training, and so on. Ideally, the use of these new techniques that would enhance the potency of actions and fortitude of effects allows leftward shifts in dose–response (DR) curves and reduces burdensome and deleterious side effects of more traditional treatment approaches.

How various neurotechnologies exert their effects and how underlying mechanisms can be better understood and exploited are of principal importance for moving toward integrated treatment approaches. One area of research that may provide a framework for how to move the field of brain stimulation forward is the field of hormesis. Hormesis is a DR model that presents an alternative to the two monotonic DR models currently used in assessing health risks, namely, the linearity no-threshold (LNT) model and the threshold model.[1-3] According to the LNT model, a toxic response is produced at any dose level—no matter how small—and is directly proportional to the dose amount. In the threshold model, toxicity results only from doses that exceed some threshold value, whereas subthreshold doses yield no effect at all. As uniquely biphasic, hormesis serves as an alternative to these two monotonic models. It is characterized not only by toxic responses to high doses and null responses to very low doses (similar to the LNT and threshold models, respectively) but also by stimulatory and (often) salutary responses to doses at levels just below the threshold of toxicity (see Figure 1).

The scientific literature contains thousands of examples that demonstrate the stimulatory and beneficial effects induced by subthreshold doses of various types of toxic agents, including ionizing radiation, chemicals, light, and even electric currents. Thus, unlike the LNT and threshold models, the hormetic model possesses a uniquely stimulatory component that may prove useful in predicting and explaining the occurrence of beneficial responses to treatments with electric currents at low,

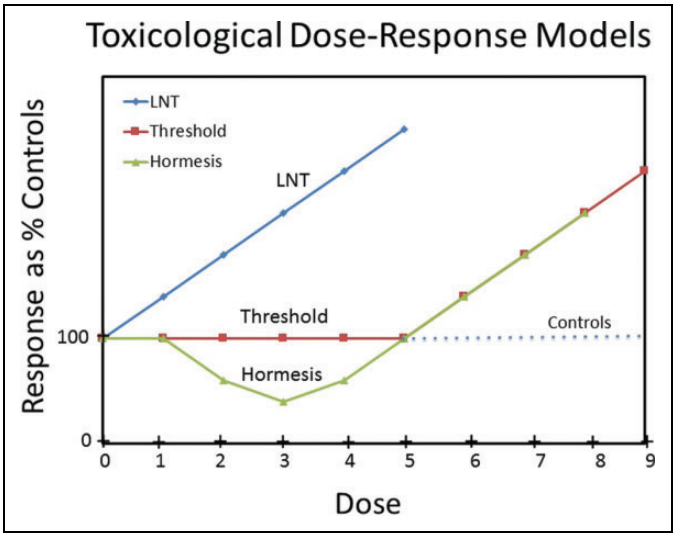

Figure 1. Schematics of the 3 major toxicological dose–response models, LNT, threshold, and hormesis, are illustrated above. Toxic responses to increasing doses of a hypothetical toxicant are represented as a percentage of untreated controls. Note that the threshold points for both the threshold and hormetic models are the same (at dose 5) and that only the hormesis model actually characterizes the observed reductions in toxicity (beneficial effects) occurring over a portion of the subthreshold range (ie, between doses 1 and 5). LNT indicates linearity no-threshold.

subthreshold doses, such as are being utilized in the development of tDCS and other neurotechnologies.[4,5] In the particular case of tDCS, its DR characteristics are known to be very similar to those of a typical hormetic stimulus, linking the two stimulations and suggesting that tDCS is simply another specific expression of the more generalized phenomenon of hormesis. In the case of both tDCS and a typical hormetic stimulus, the doses are small enough to be considered safe (subtoxic) and the responses are very frequently (but not always) considered beneficial. Since beneficial responses in each case are usually modest in intensity (amplitude) and easily masked by baseline noise, DR research protocols for both tDCS and a typical hormetic stimulus require greater statistical power (larger sample sizes) and less individual variability among test populations (greater homogeneity), enhancing sensitivity and, thus, enabling detection of a modest hormetic response.[6,7] Such similarities in DR characteristics seem to indicate that tDCS-induced responses are very likely hormetic.

Although initially not very well known and also very controversial, the concept of hormesis has become more broadly recognized and has gained steady acceptance by the scientific community. This is due in large part to the research efforts of Edward Calabrese and his many collaborators at the University of Massachusetts at Amherst. In the past 20 years, Calabrese and colleagues have created two hormesis relational databases, one for ionizing radiation and the other for chemicals (containing well over 10,000 examples of chemical hormesis) and have used them to assess and validate various aspects of hormesis.[7-9] In over 150 peer-reviewed publications, they have shown that

the concept of hormesis applies to many different classes of stimuli (eg, chemicals, ionizing radiation, heat, pressure, etc), functions across all plant and animal species and all levels of bioorganization (from cells to whole organisms), and affects a broad range of biological end points. Statistical analytical studies conservatively argue that at least 40% of all chemicals are hormetic and that the true default DR model is in fact hormesis.[10-14] Qualitative and quantitative assessments indicate that the optimal hormetic dose for toxic agents occurs at a low dose range and is always below the toxicity threshold.[3] Mechanisms have been documented for hundreds of hormetic responses,[3] and a modern popular toxicology textbook now references and describes hormesis as a legitimate alternative to current DR models.[15] Moreover, Calabrese has recently shown[16,17] that adaptive and preconditioning responses, which are readily accepted and broadly utilized by the scientific and medical communities because of their great promise in the treatment and prevention of diseases, are simply manifestations of hormesis. This important finding underscores hormesis as a foundational concept in understanding DR phenomena, lends greater credence to the authenticity and utility of the hormetic model, and, most importantly, strongly suggests exploiting hormesis (and knowledge of its stimulatory phase) for the purpose of developing various novel interventions, such as tDCS, for use in the cure and prevention of physical and mental diseases, as well as in the enhancement of normal cognitive functions.

Low levels of ionizing radiation are also known to stimulate beneficial (hormetic) responses,[18] suggesting the possibility that low levels of nonionizing radiation, such as light, radiofrequency radiation, and electromagnetic fields, may evoke similar beneficial (hormetic) responses. Indeed, evidence is now appearing in the literature supporting the idea that nonionizing radiation at low doses can modulate biological responses in cells.[19-23] In view of this exciting possibility, and the fact that hormesis has now been authenticated for chemicals and ionizing radiation, the AFOSR has initiated new research to explore the possible hormetic effects of nonionizing radiation. This research includes (1) the development of a relational database at the University of Massachusetts on nonionizing radiation-induced hormesis and (2) animal and human investigations at the Air Force Research Laboratory[24,25] to explore the behavioral and cognitive effects induced by one specific form of nonionizing radiation, transcranial electrical stimulation (tES). As tES can be administered to the brain as either an alternating, oscillating, or direct electrical current, the Air Force has chosen to utilize direct current in its initial research efforts since to date most of the fundamental and applied research in the tES area has been conducted using tDCS technology.[6]

Transcranial direct current stimulation has been used to investigate the effects of low doses of electrical currents on modulating behavior, cognition, and performance in animals and humans and on the molecular and cellular mechanisms by which these effects may be mediated. The effects of tDCS on improving learning[26-29] and memory[30-32] and on mitigating depression,[33,34] chronic pain,[35,36] fatigue,[37] are of immediate interest to the Air Force. In addition, tDCS has also been reported to improve stroke recovery times[38,39] and symptoms of a number of psychiatric disorders,[40,41] suggesting the further possibility that military-related neuropsychiatric pathologies, such as post-traumatic stress disorders and traumatic brain injuries, may offer other opportunities to apply tDCS technology.

Toward Elucidation of Mechanisms: Key Questions

Most experimental research in the area of tDCS currently focuses on behavioral effects and, as such, tends not to address the neural mechanisms involved in mediating these effects. In view of this gap in understanding, the primary goal of the Air Force planning meeting was to develop a research strategy that will help to elucidate the fundamental cellular and molecular mechanisms involved in tDCS. That tDCS appears to be nontoxic and yet optimally effective at negligibly small current strengths (1-2 mA) strongly suggests a possible hormetic mechanism. As a result, the knowledge acquired from the expanding hormesis databases offers opportunities to generate insights, hypotheses, and guidance for expanding our understanding of the cellular and subcellular mechanisms of tDCS. Specifically, the hormesis model suggests that future tDCS research could benefit by identifying (1) the optimal stimulatory dose for each individual (including frequency, intensity, duration, pulse characteristics, etc), (2) the specific brain sites (and networks) to be targeted to evoke the desired response, and (3) the specific cellular components that mediate the response. Adopting these research suggestions would imply the need to develop biomarkers for use in determining the optimal tDCS treatment dose on an individual basis and a technique/device for accurately delivering a measured dose to a specific area of the brain.

Ultimately, the vision and hope are that tDCS research—enabled by hormesis—will produce acceptable, noninvasive, safe, quick-acting, and long-lasting treatments and/or optimizations of neurocognitive and behavioral functions that, unlike pharmacological agents, can target specific tissues and neural networks with minimal or no deleterious side effects.

To help advance discussion relevant to the goals of the Air Force planning meeting, the following questions were used to prompt and guide discussions:

1. What is the current state of knowledge concerning tDCS?
2. What new knowledge will advance mechanistic understanding of tDCS?
3. What barriers are preventing acquisition of this new knowledge?
4. How can these barriers be overcome or eliminated?
5. What role(s) can theoretical modeling play in understanding mechanisms?
6. How are theoretical and experimental approaches integrated, and how should such integration be fortified in future studies?

7. What equipment and personnel needs are necessary to realize such integration?
8. How are dosimetry requirements determined?

Putative Mechanisms of tDCS (Marom Bikson, Michael Nitsche)

Over the past 15 years, animal and human studies of basic mechanisms of tDCS[42] have identified some major physiological effects, such as subthreshold polarization of neuronal membranes[43,44] and glutamatergic plasticity. Such effects involve spontaneous neuronal activity adjunct to DC-induced membrane polarization[45,46] and regional plasticity effects on cerebral networks.[47,48]

The rigor of these experiments has established a basis for designing interventional strategies to enhance learning and performance and to treat neuropsychiatric disorders. Many clinical trials are based on dose parameters (1-2 mA, 20-30 minutes) that have been shown experimentally to produce lasting changes in brain excitability. These same clinical neurophysiology studies have shown a nontrivial DR function and interactions with ongoing tasks and chemical agents.[49-51] Based on experimental data, theories have been advanced to explain tDCS mechanisms, although we currently lack an explanatory framework that has been accepted by the tDCS research community. In fact, a majority of trials with tDCS are rationalized simply by placing the electrode "over" a target region and assuming based on the polarity of the electrode (anode or cathode) that "brain function" will be altered (boosted or inhibited). This rationale ignores the complexity of tDCS dose, issues regarding the physics of brain current flow,[52] complex relations between cortical activity and performance, and treats higher cognitive function and disease as a "sliding scale" rooted in 1 brain region.

There remains a gap between data collected on tDCS mechanisms in animals and humans[45,53,54] and the development of a comprehensive mechanistic framework that explains how tDCS can be optimized (eg dose, high-definition tDCS)[55] for a given indication or individual.[56] Reliable methods to predict and correct for interindividual differences are lacking.[57,58]

Clinical trials (using a range of doses) should be part of an ongoing effort to collect data for a mechanistic model.[59,60] Central to this endeavor are (1) new tools (biomarkers) to measure and titrate the effects of tDCS in both animals and humans,[61,62] (2) a framework to relate findings on neurophysiological responses to tDCS to cognitive functions and behaviors, and (3) definition of optimal practices that would ensure reproducibility of tDCS-induced effects in both research and translational (clinical and/or paraclinical, eg, occupational) use.[63-65]

Types of Stimulation (Michael R. Hamblin, Michael Nitsche)

A variety of brain stimulation methods can be derived, which differ in regard to the physical properties of the induction procedure. The term "noninvasive" brain stimulation refers to those techniques that act on brain physiology without the need for surgical procedures involving electrode implantation (such as deep brain, direct cortical, or epidural stimulation techniques). The main group of noninvasive stimulation techniques affects brain function via electrical or magnetic impulses. However, laser stimulation, transcranial ultrasound, and tonic magnetic fields have also been shown to affect brain physiology.

Conventionally, stimulation techniques that primarily induce activity of neurons (suprathreshold stimulation) are distinguished from those that primarily exert modulatory effects on ongoing neuronal activity and excitability (subthreshold). The first group includes high-intensity short-pulse tES, transcranial magnetic stimulation (TMS), electroconvulsive therapy, and paired associative stimulation (PAS). The second group includes forms of low-intensity (eg, few mA) and sustained (eg, minutes) tES, such as tDCS, transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). The electric field intensities produced in the brain by suprathreshold techniques are often 2 orders of magnitude above subthreshold,[52,66-70] allowing for triggering of action potentials.[71] However, it is important to recognize that so-called suprathreshold techniques ultimately affect behavior by modulation of endogenous networks,[72,73] whereas the so-called subthreshold techniques can influence firing in the active system.[74] For a comprehensive classification of tES techniques, see Guleyupoglu et al.[75]

Transcranial electrical stimulation using high-intensity short pulses was introduced in 1980 and was the first noninvasive brain stimulation technique shown to alter activity in the human cerebral cortex.[76] An electrical stimulus between 300 and about 1000 V is applied for a few milliseconds via the intact skin over the target region. Sufficiently strong stimulation results in the activation of neurons in the target area. One disadvantage of this stimulation technique is that it also activates excitable structures in the skin between the electrodes and the target, and thus, this stimulation is relatively painful.

This problem is circumvented by the use of TMS, which induces electrical current flow in the brain via magnetic induction based on Faraday law, delivered through a magnetic coil placed on the head.[77] This procedure is relatively painless in comparison. Recently, more sophisticated stimulation protocols have been developed, which allow relatively selective activation of pharmacologically characterized neuronal subpopulations, such as glutamatergic, GABAergic, and cholinergic neurons.[78,79] Beyond these stimulation protocols that induce solely acute activation of target neurons, stimulation protocols have been developed which result in alterations in cortical excitability that outlast the stimulation (ie, to induce neuroplasticity). One of these techniques is repetitive TMS (rTMS), in which trains of magnetic stimuli induce long-term potentiation (LTP)– or depression-like alterations in neuronal excitability. Similar to animal experiments, slow stimulation (stimulation frequency $\leq$ 1 Hz) induces excitability diminutions, whereas high-frequency stimulation (>1 Hz) induces excitability

enhancements. Recently, new stimulation techniques such as θ-burst stimulation or quadripulse stimulation have been developed, which are aimed to induce more stable and longer-lasting effects.[80]

A qualitatively different protocol is PAS. In this study, a peripheral nerve stimulus is combined with a central nervous system stimulus. The standard protocol encompasses motor cortex plasticity induction via a combination of motor cortex TMS and stimulation of a peripheral nerve of the upper limb. Dependent on synchronous or asynchronous arrival of both stimuli the targeted motor cortex, LTP-like (synchronous) or LTD-like (asynchronous) plasticity is induced, which share some aspects with spike-timing-dependent plasticity and has been well explored in animal experiments.

Tonic stimulation with direct currents (eg, tDCS) can be discerned from oscillatory stimulation techniques (eg, tACS, tRNS). All of these stimulation techniques encompass positioning at least 2 stimulation electrodes on the body; for brain stimulation protocols, at least one of the electrodes is placed on the head. Generally, electrodes are relatively large (between 25 and 35 cm^2), and stimulation intensity varies between 1 and 3 mA.[81] However, new protocols that encompass more focal (eg, high-definition tDCS) or network stimulation by use of multiple target electrodes are available.[52,82] The direction of respective activity and alterations in excitability depend on the direction of electrical current flow in relation to neuronal orientation. The use of tRNS with frequencies between 100 and 600 Hz induces similar neuroplastic effects, in which direction depends on stimulation intensity.[83] To date, it remains unclear whether tRNS alters oscillatory brain activity. Alteration in spontaneous oscillatory activity can be accomplished through tACS, which in the main frequency bands of physiological brain activity does not induce plasticity. However, stimulation in frequency bands above 100 Hz up to low kHz frequencies has been shown to induce LTP-like plasticity.[84]

Transcranial near-infrared (tNIR) light therapy is a relatively new approach for treating brain disorders and possibly for enhancing cognitive function.[85] It is derived from low-level laser (light) therapy (LLLT, also known as photobiomodulation), which has been studied since 1967 (see Chung et al[86] for a review). Low-level laser (light) therapy has been mostly used to stimulate wound healing, to reduce pain and inflammation, and to preserve tissue at risk of necrosis. The mechanism of action of LLLT is thought to involve absorption of red or near-infrared photons by cytochrome C oxidase (unit IV of the mitochondrial respiratory chain).[87,88] This photon absorption may dissociate inhibitory nitric oxide,[89] thereby allowing respiration to resume unhindered and adenosine triphosphate (ATP) synthesis to increase.[90] Various signaling molecules are activated, including (but not limited to) reactive oxygen species, cyclic adenosine monophosphate (cAMP), nitric oxide (NO), and calcium (see Figure 2; Alexandratou et al[91]).

Retrograde mitochondrial signaling may also play a major role in the response to light.[92] Many transcription factors have been shown to be activated and have been proposed to account for the long-lasting effects of light exposure.[20] Recently, light-sensitive ion channels such as the transient receptor potential vanilloid channel have been suggested to be involved in cellular mechanisms of LLLT action.[93]

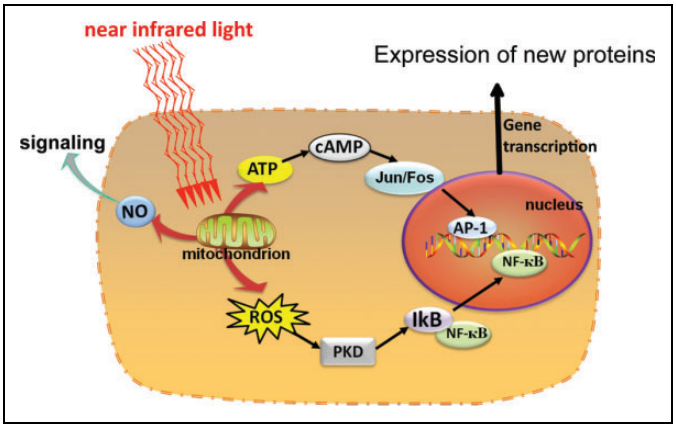

Figure 2. Mechanism of action of LLLT at a cellular level. Near-infrared (NIR) light is absorbed in mitochondria, leading to the activation of signaling pathways (cyclic adenosine monophosphate [cAMP], reactive oxygen species [ROS], NO) that in turn activate transcription factors such as nuclear factor kappa B (NF-kB) and activator protein 1 (AP1) (see text for details). LLLT indicates low-level laser (light) therapy; NIR, near-infrared; ROS reactive oxygen species.

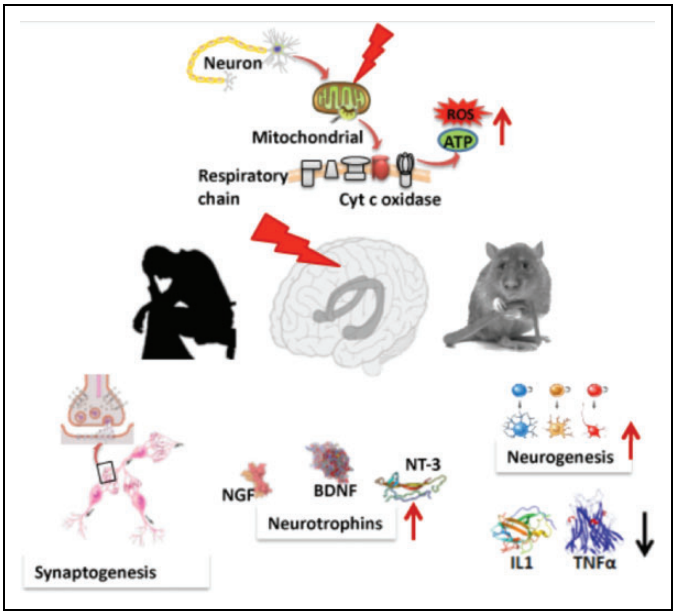

Figure 3. Mechanism of action of tNIR in the brain. The transcription factor activation as discussed in Figure 1 leads to upregulation of neurotrophins such as BDNF leading to neuroplasticity (synaptogenesis) and newly formed neurons (neurogenesis). Neuroinflammation is reduced. BDNF indicates brain derived neurotropic factor; IL-1, interleukin 1; NGF, nerve growth factor; TNF-α, tumor necrotic factor α; tNIR, transcranial near-infrared.

The use of tNIR as an intervention started with studies using LLLT after induction of stroke in animal models.[94] Promising results in 2 different animal models (rats and rabbits) led to a series of clinical trials.[95] The first trial was

successful,[96] the second had mixed success,[97] whereas the third trial failed to meet its interim end point and was therefore discontinued for futility.[98] Nevertheless, the relative success of at least some of these studies prompted researchers' continued investigations of the effects of LLLT in acute TBI in animal models.[99] From such work, a number of positive results have now been reported. There is building evidence to support that tNIR can stimulate neurogenesis as shown by induction of bromodeoxyuridine (BrdU)-positive neuroprogenitor cells in the dentate gyrus and subventricular zone of laboratory animals.[100] Moreover, tNIR can stimulate synaptogenesis or neuroplasticity as shown by upregulation of synapsin-1 in the cortex of mice with TBI (see Figure 3; Xuan et al[101]).

The use of tNIR is currently being studied as a possible approach to treating neurodegenerative disorders such as Alzheimer dementia[102] and Parkinson disease,[103] and clinical studies are currently underway that examine the potential for using tNIR to treat psychiatric disorders such as major depression[104] and cognitive and emotional effects of TBI.[105]

Yet, it may be premature to consider tNIR as a form of noninvasive brain stimulation in the same way as described for tDCS and rTMS. There appears to be both several similarities as well as several differences between these approaches. Similarities include the fact that tNIR and tDCS and rTMS have been used for cognitive enhancement in normal (nondiseased) subjects. Transcranial near-infrared has been used to improve memory in mice[106] and improve cognitive function[107] and mood[108] in healthy human volunteers. Both LLLT[19,109] and tDCS[110] techniques appear to exert hormetic effects.[111] Such hormetic effects were shown in a recent study of tNIR for TBI in mice: 3 daily LLLT treatments were shown to produce better outcomes in terms of neurological severity score and Morris water maze performance than either a single treatment (4 hours post-TBI) or 14 daily LLLT treatments (1 a day for 2 weeks post-TBI).[112] As previously noted, tNIR can stimulate brain-derived neurotrophic factor (BDNF) and synaptogenesis in mice,[101] but the effect was most pronounced at a long time point (4 weeks) post-tNIR treatment.

Differences between LLLT and tDCS include the fact that there is little evidence to date that tNIR produces direct neural activity. To our knowledge, there have not been any studies that have shown that tNIR induces LTP or LTD in ex vivo brain slices. It is clear that tDCS- and rTMS-induced cognitive enhancement has been studied much more than the same effects produced by tNIR. Yet, we believe that it is fair to say that the mechanism of action of tNIR is better understood than the mechanism that may putatively be involved in the effects of tDCS. Clearly, further research will be required to better elucidate the mechanisms and relative effectiveness of these approaches in producing defined neurocognitive and behavioral outcomes.

Animal Models (Ryan Jankord, Marom Bikson)

As previously noted, it is not in any way a novel idea that neural activity can be modulated by an externally applied electrical field. It was almost 60 years ago that Terzuolo and Bullock[113] used the abdominal receptors in the crayfish and the cardiac ganglion of the lobster to study neural modulation by an electric field. From their observations, these authors concluded that (1) active neurons are sensitive to small electric fields; (2) a static electrical field can modify the frequency of neural firing; (3) higher electric fields are required to cause a silent neuron to fire than to modulate the function of an active neuron; (4) the orientation of electric field relative to neuronal morphology (axis of polarization) determines whether firing is accelerated or inhibited; and (5) there is an optimal axis of polarization, and rotation of this axis changes the amount of electric field required to induce a similar response. These results were among the first to demonstrate that electrical stimulation can have immediate and profound effects on neural activity and established the foundation for subsequent studies that investigated these factors.[43,114,115]

In addition to the immediate effects of electrical stimulation, Bindman et al[116] demonstrated that a polarizing current delivered for at least 5 minutes resulted in long-lasting changes in evoked and spontaneous activity that continued for several hours. These authors noted that "... it is possible to produce a long-lasting change in the activity of the brain by means of a very small temporary alteration in the physical environment of the nerve cells." These early experiments demonstrated that electrical simulation has both immediate effects on neuronal activity and can also induce effects that persist beyond the cessation of electrical stimulation. The requirement for sustained (eg, on the order of minutes) stimulation to produce lasting changes informed the studies of Nitsche and Paulus[117] and prompted modern tDCS protocols to continue to employ sustained stimulation.

Many studies subsequent to Terzuolo and Bindman's work have contributed to the current understanding of how neural function can be modulated by extrinsic stimuli. One area of particular relevance is the study of LTP,[118] a mechanism by which tDCS is thought to modulate brain function. Studies of rodent brain slices in vitro have demonstrated that direct current stimulation can affect LTP[53] and that the effect of stimulation on LTP was dependent on *N*-methyl D-aspartate and BDNF.[45] More recent studies in rabbits have shown that tDCS may modulate presynaptic mechanisms of transmission.[119] In addition, sustained direct current has also been shown to produce acute and lasting changes in oscillations in brain slices.[54] Thus, it will be important for animal studies to further characterize molecular mechanisms underlying tDCS-induced LTP and specifically address how low-intensity stimulation is amplified and why sustained currents are needed.

One of the many advantages of animal models is that behavioral changes can be both correlated with underlying neurobiological mechanisms and translated to clinical populations. For example, it has been shown that the application of tDCS over the frontal cortex improves working memory and skill learning in rodent models.[120] Furthermore, tDCS exerts beneficial effects on neural plasticity and motor function in rodent models of stroke injury, suggesting an influence upon both neural structure and function.[121] In a rat model of cognitive dysfunction, tDCS has

also been shown to promote the recovery of motor behavior.[122] These studies reveal considerable modulatory effects of tDCS and raise the possibility that tDCS may have the potential to provide therapeutic benefits in a number of neuropsychiatric conditions, as well as to improve performance in a variety of neurocognitive and behavioral tasks.

Effects of tDCS on Cognitive Function and Performance (R. Andrew McKinley, James Giordano)

There is a growing body of literature suggesting that noninvasive brain stimulation techniques, including certain types of tES (eg, tDCS and/or tACS), can modulate brain activity in ways that benefit aspects of cognition that are directly related to learning, acquisition, and performance[123-125] (see McKinley et al[126] for review). A number of career fields require human operators to engage and/or monitor manual and highly automated systems. Repetitive tasks and those that require sustained vigilance and attention demand considerable effort to maintain over long periods of time. Humans are not particularly skilled at maintaining long-term vigilance. In fact, a phenomenon known as the "vigilance decrement," which is characterized by a linear decrease in the number of critical signals recognized over time or an increase in reaction time,[127] has been well documented in the literature since the 1960s.[128] Depending on the frequency of the visual stimulus and the target stimulus, this decrement can be observed in as little as 20 minutes.[129] This tendency to miss a greater number of critical signals or targets over time can have profound consequences in both civilian and military professions that need to maintain high levels of vigilance over long periods of times to protect human lives from potential danger (eg, air traffic control operators, security personnel, intelligence analysts, baggage screeners, etc).

Recent findings support that tDCS may be well suited to mitigating decline in human cognitive capacities necessary for the performance of tasks requiring sustained attention. Nelson et al[130] provided evidence that tDCS applied over either the left or right dorsolateral prefrontal cortex (DLPFC) eliminated the vigilance decrement in a 40-minute task trial. Vigilance decrement is typically accompanied by a linear decline in blood flow velocities within either the left or right middle cerebral artery.[129] Nelson et al[130] indicated that tDCS attenuated this decline in blood flow velocity and increased regional cerebral oxygen saturation.

Moving the anode location from the scalp site directly over left DLPFC to a more caudal location (ie, over the left frontal eye field) produced similar effects on vigilance performance.[131] This study also presented evidence that tDCS produced changes in oculometrics, such as eye blink rate and percentage of eye closure. The authors concluded that these changes were indicative of more eye movements and hence reflected subjects' more thorough searching of (ie, increased attentiveness to) the visual scene.

The improvements in attention and visual search have more recently been shown to enhance multitasking performance.[132] The data suggested that tDCS led to a significant increase in information throughput (ie the amount of stimuli to which the participant could respond) over the entire range of difficulty levels tested. When examining performance in the individual tasks, the tasks that tested attention/vigilance were enhanced to the greatest extent. Tasks such as tracking and audio communications did not exhibit a large effect. Thus, the results help reinforce the idea that tDCS applied over the left DLPFC preferentially affects sustained attention.

The effects of tDCS on vigilance have also been observed on much longer time lines in sleep-deprived research participants. Using the tDCS paradigm of Nelson et al,[132] McIntire and coworkers[37] demonstrated that tDCS mitigated the vigilance decrement for at least 6 hours—3 times longer than the effect of caffeine. Additionally, both tDCS and caffeine led to improvements in reaction time and fewer lapses on a simple reaction time task, both of which are highly sensitive to fatigue. Subjective reports revealed that participants receiving tDCS experienced less fatigue and/or drowsiness and more energy following stimulation as compared to subjects who received sham tDCS. A follow-on study examined these effects when tDCS was applied 10 hours earlier in the sleep deprivation period.[133] The results confirmed that tDCS prevents declines in vigilance performance for approximately 6 hours poststimulation. However, the effects on arousal and mood were found to persist much longer (at least 24 hours post-tDCS). These findings suggest that it may be possible to administer tDCS before the start of the shift to provide performance benefits that last the duration of the shift.

Transcranial stimulation-induced changes in attention are also believed to influence learning. Clark et al[134] found that anodal tDCS applied on a scalp location over the right ventral lateral cortex facilitated training in a threat detection task. Participants were asked to identify threats such as trip wires and sniper shadows in simulated combat theater (ie, dismounted soldier) settings. These findings, later replicated by Falcone et al,[135] revealed that improvements in threat detection performance persisted for at least 24 hours following tDCS. McKinley et al,[29] using the same tDCS montage employed by Clark and colleagues,[134] demonstrated facilitated learning in a threat detection task involving identification of threats in simulated synthetic aperture radar imagery. Both Clark et al[134] and McKinley et al[29] posited that tDCS may modulate attention during training, thereby improving learning. Simply put, the more information that can be attended to during training, the more that can be encoded and subsequently remembered. However, information that is focal to attention is not necessarily engaged in/by processes of memory.[136,137] Procedural memory has also been shown to benefit from tDCS applied to the left DLPFC.[138]

Participants were trained to identify targets as "friends" or "foe" in a gaming simulation called "Warship Commander," which was developed by the US Navy. The task requires participants to learn a series of button presses that must be performed quickly and in the correct order to maximize their score. Participants who received cathodal tDCS over the left DLPFC during memory consolidation (ie, immediately after training) performed significantly better 24 hours later than

subjects who received either sham tDCS or anodal tDCS over the motor cortex during training. Nondeclarative and declarative memory systems are competitively interactive[139,140]; therefore, it is believed that cathodal tDCS reduced activity in brain networks typically engaged in declarative memory (ie left DLPFC). This, in turn, disinhibited procedural memory systems during the consolidation process.

Cognitive performance effects of tES are highly context dependent.[141,142] Individual traits (eg, age, gender, hormonal levels, brain state and network excitability, and/or inhibitory tone), as well as specific aspects of environment and task(s), all affect and can alter response to noninvasive neuromodulation.[50,51,143,144] This is crucial to note when considering how tES may (a) be dependent upon brain state for effect; (b) differentially affect neural nodes and networks active in learning, memory, vigilance, and attention; and (c) be utilized and employed in practical settings to facilitate and optimize these cognitive and behavioral functions.

Understanding how tES engages and affects neural function is important to the development of improved methods. A number of putative mechanisms of tDCS-induced changes in behavior and performance have been proposed. It has been posited that anodal tDCS affects cerebral metabolic activity, based upon studies that have shown increased glutamate, glutamine, and *N*-acetyl aspartate (NAA) levels produced in parietal cortical loci both proximal and contralateral to application of 2.0 mA tDCS (30-minute treatment).[145] Nonlocal, more global cerebral effects have also been described.[146] Because the tDCS paradigms described by McKinley et al,[29] Nelson et al,[130,132] and McIntire et al[37] used an extracephalic cathode placement on the contralateral biceps, it is possible and even likely that the applied current either incurred a peripheral to central effect and/or modulated activity in areas of the brain stem, including the reticular magnocellular nuclei, thereby inducing increased supraspinal noradrenergic activity. It has been speculated that glutamatergic–noradrenergic interactions (ie, glutamate amplification of noradrenergic effects) may be involved in eliciting cortical ''hot spots'' that represent increased nodal and network functions important to attention, learning, and memory.[147] It is also possible that neuromodulatory effects involve activation of glial mechanisms.

Application of tDCS over the right motor cortex caused a significant increase in fractional anisotropy (FA) in the right inferior longitudinal fasciculus and right internal capsule lying beneath the anode. The change in FA was due to alteration in radial, but not axial, diffusivity. This change in FA was likely caused by modification of white matter (ie, a change in myelination). Increased myelination would potentially improve efficiency of signal transmission within and between nodes in neural networks[148] (a more detailed discussion of putative mechanisms of tES is provided elsewhere in this paper).

In sum, the aforementioned studies suggest a promising role of tES in human performance optimization. Further research will be required to more accurately define how individual and environmental variables interact to affect the outcome(s), viability, and value of specific neuromodulatory approaches.

Clinical Applications of tDCS and the Importance of Elucidating Mechanisms (Roy Hamilton, Vincent P. Clark)

Recent years have seen an explosion of interest in clinical applications of tDCS, including but not limited to the fields of neurology, psychiatry, physiatry, and pain management.[42] The practical advantages of using tDCS as a therapy are readily apparent—it appears to be safe and is tolerable, inexpensive, relatively simple to operate, and easy to combine with other treatments. For these reasons, it is being investigated as both a replacement therapy for pharmacologic and other treatments that are intolerable, ineffective, unavailable, or prohibitively expensive and as an adjunctive approach to enhance the efficacy of existing medications and behavioral therapies. For example, recent meta-analyses have shown that active tDCS was effective in reducing major depression when compared to sham tDCS,[149] for reducing neuropathic pain after spinal cord injury[150] and also for improving cognition in age-related dementia.[151]

However, as more of this work emerges, it is becoming increasingly clear that improved understanding of the basic mechanisms of tDCS is needed in order to truly advance its use in clinical populations, as well as to ensure its long-term safety. Other meta-analyses have shown small or inconsistent effects or a lack of significant effect for other clinical populations, such as for certain aspects of recovery from stroke.[152,153] Such failures may have resulted from uncertainty regarding the mechanisms of tDCS. In the absence of this type of knowledge, two fundamental therapeutic questions will remain largely unanswered—What is the most effective way to stimulate the brain with tDCS? and What are the most likely intended and unintended outcomes of stimulation?

It is widely understood that a variety of stimulation parameters dictate the behavioral effects of tDCS, including but not limited to electrode number, location, size, and polarity, as well as stimulation intensity and duration.[154] For cognitive functions, recent evidence also suggests that the task one is engaged in during tDCS significantly impacts the effects of stimulation.[50] To a first degree of approximation, these parameters align conceptually with known cellular and interneuronal mechanisms of tDCS. For instance, the depolarizing effects of anodal tDCS on neuronal resting membrane potentials[71] and its demonstrated influence on LTP in neuronal circuits[53] provide some account for the observed excitatory effects of anodal stimulation on motor physiology and behavior. However, further exploration of these parameters reveals important gaps in our understanding of tDCS mechanisms. For instance, the effects of stimulation do not follow simple linear DR relationships.[49] Moreover, anodal and cathodal stimulation are not synonymous with excitatory and inhibitory stimulation with respect to their effects on neural function and behavior.[49,155] In short, our current understanding of tDCS effects at the level of the cell does not map neatly onto complex behaviors, underscoring the need for better characterization of the principles and properties that govern functional relationships at the level of the cell, circuit, network, and system.

This process of characterization will also permit clearer predictions of which individuals are likely to benefit from stimulation, which disease processes are likely to be most amenable to treatment, and what some of the long-term intended and unintended consequences of stimulation are likely to be. The latter issue is especially relevant when considering how applications of tDCS in clinical populations are likely to be used to inform potential interventions to enhance performance in otherwise healthy populations. Evidence suggests that stimulation applied with either inadequately considered parameters or to the wrong population(s) of individuals could result in inadvertent deleterious effects on cognition and performance, at least acutely under experimental conditions.[51] Research that allows a more thorough, finely granular understanding of the biological and neural effects of tDCS will allow better prediction and monitoring of undesired cognitive and functional effects that may arise from stimulation, and will help to prevent or at least minimize potential deleterious cognitive effects.

In conclusion, clinical investigations employing tDCS have undergone tremendous expansion in recent years and are producing some promising results for certain clinical populations. However, the effectiveness and utility of this technology in the clinical arena are ultimately constrained by limitations in understanding of its basic mechanisms. Perhaps, in light of this paucity of mechanistic understanding, few clinicians employ tDCS in clinical practice, and the limited number of clinicians who do tend to rely on reductive and oversimplified concepts to guide how stimulation should be applied and to whom. Thus, many patients are unable to access tDCS in clinical care. To some extent, this has fostered a ''do-it-yourself'' movement among prospective patients (and more broadly within the general population, with goals of cognitive performance optimization), which has become the subject of considerable attention and some concern.[156] Clearly, this is a field in which further mechanistic discoveries at the bench will translate into important advances and refinements at the bedside and possibly beyond.

Roles of DR and Hormesis Concepts in Elucidating Mechanisms of tDCS (Edward Calabrese, H. Branch Coslett, Rachel Wurzman)

As noted, there is an urgent but as yet unmet need for additional and ever more detailed information regarding parameters of tDCS. Lack of such information (eg, about optimal current intensity and duration) has delayed the advancement of theoretical and experimental foundations of research into the mechanisms of action of tDCS and, ultimately, the translation of tDCS to use in clinical and occupational settings. Dose–response relationships for tDCS have been difficult to identify for a number of reasons.

First, in the case of tDCS, dose is not a simple measure. Instead, tDCS dose is defined by multiple factors, including current strength, electrode size, stimulation site, polarity, duration of stimulation per session, and frequency and number of sessions. Interactions among these variables are likely to be complex and unequally relevant for different tDCS mechanisms investigated. For example, the duration of stimulation is the factor most relevant to the DR relationship model.[157] Hormesis therefore has the advantage of being a generalizable model for relating tDCS dose to response for multiple mechanisms located across many different levels of brain organization, which could prove especially valuable for the development of predictive DR models needed to advance the field.

Second, tDCS influences the nervous system at multiple levels and possibly at multiple timescales. Unlike pharmacological agents in which the response of brain network activity can be considered downstream of effects at the cellular and subcellular levels (eg, through receptors that mediate changes in cell membrane excitability or gene expression), the physical effects of tDCS (eg, the polarization of cellular membranes in the path of current flow, as discussed elsewhere in this article) may exert independent, direct effects at each of these levels.[42,74,158] Consequently, tDCS may influence neural function in the short term through bottom-up effects of neuronal and synaptic activity, as well as by top-down effects of neuronal network dynamics,[159,160] which further constrain any additive effects of tDCS at synapses. Moreover, because such changes in the patterns of neural activity can be self-reinforcing, adaptive processes following an additional disruption to homeostasis are likely to be relevant to both the immediate and short-term responses as well as the long(er)-term responses to tDCS (in some cases, up to several months later).

Third, measures of the effect of tDCS are limited. Although there is some information from electrophysiologic, imaging, and pharmacologic studies, most data describing the effects of the intervention are behavioral. Given the complex relationship between behavior and function at various levels of the nervous system, the effects of tDCS at the synaptic level may be difficult to determine because the available measures of response (eg, on cognition or behavior) are several levels removed from the site of the direct effects of tDCS. A better understanding of the mechanisms and effects of tDCS at synapses, cells, circuits, networks, and behavior may help in the cross-application of DR activity occurring at different levels of hierarchical brain organization.[42] However, in order to realize the potential of tDCS to provide effective clinical treatments, alter human performance, and/or enhance cognition, a more synthetic understanding of DR relationships for tDCS that spans organizational levels and mechanisms will be required. This information will also be crucial to developing guidelines that can inform rational design of tDCS applications to produce specific outcomes.

Applying the framework of hormesis to tDCS dosimetry may be useful. In contrast to linear or linear threshold-based DR models, which describe monotonic response past a threshold dose (zero and nonzero, respectively), the hormetic DR model describes a varying, biphasic response that only becomes monotonic outside the dose range delineating the adaptive response. The typical shape of hormetic DR curves is bimodal, with upright or inverted U- or J-shapes representing low-dose stimulation and high-dose inhibition (or vice versa).

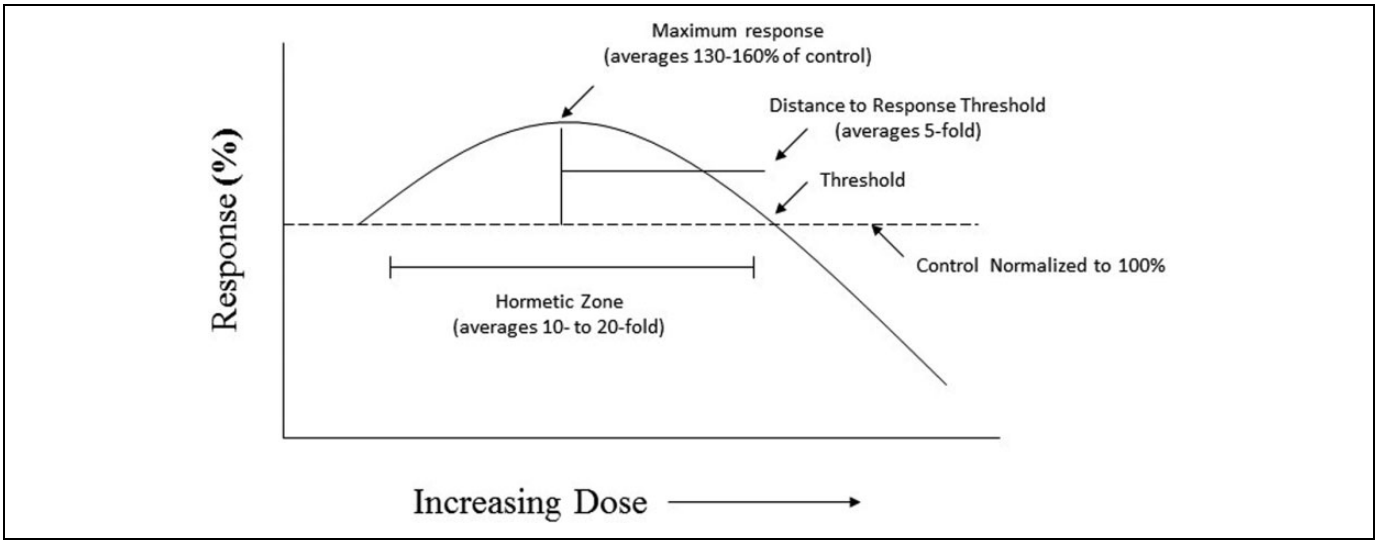

Figure 4. Hormetic dose–response curve depicting the quantitative features of hormesis.

The stimulatory phase at the low dose range of the biphasic hormetic DR can occur through direct stimulation or through a compensatory response to homeostatic perturbation. Additionally, hormetic DR models apply to the effects of a preconditioning dose. In this light, tDCS may be considered to be analogous to a preconditioning stimulus that modulates the neural system's sensitivity to subsequent effects of neuronal activity on synaptic plasticity[161] or to further exposures to tDCS.[162]

Hormetic DR models were conceived in toxicology to explain the paradoxical protective effects of very low doses of a toxin. In that context, perturbation of a system's homeostasis by an agent that would be harmful at high doses instead stimulates a ''compensatory'' or protective response at very low doses (see Figure 4). As long as the effects of the stimulated ''compensatory'' response exceed the magnitude of the effects of the dose's ''direct perturbation,'' the effect on the response is stimulatory. Exceeding the optimum dose required to activate the compensatory mechanism, the magnitude of the perturbation (ie, the dose) then opposes stimulation of the ''compensatory'' response until a minimum response threshold is reached (ie, the hook of the inverted ''J,'' as shown in Figure 4), beyond which point there is no further compensation for dose perturbation of the system; the direct effects of the perturbation simply accumulate with dose (ie, the ''stem'' of the inverted ''J'').

Using this framework, the neuromodulatory effects of tDCS can be analogously described in terms of an adaptive response, except that the classifications of mechanisms engaging the ''direct perturbation'' versus ''compensatory effect'' are reversed. Simply, the mechanism for DR to tDCS is the synaptic plasticity itself, which is an adaptive response triggered by cumulative perturbation of ongoing neuronal activity over time during stimulation. Mechanisms for tDCS effects still operate within a hormetic dose range, except that it is defined by the cumulative time of stimulation prior to the onset of neuroplasticity, rather than the cessation of compensatory activity.

The effects of tDCS are reflective of hormetic effects in several respects. First, nonlinear DRs to tDCS have been observed in the motor system. In particular, cathodal tDCS decreased corticospinal excitability at 1 mA but significantly increased corticospinal excitability at 2 mA, without any change in polarity or position of the stimulating electrodes.[49] This suggests that the tDCS mechanism is active in a hormetic response range. Second, tDCS incurs effects despite current amplitudes incapable of directly generating a neuronal response. This supports the possibility of a hormetic response. Third, the magnitude of tDCS effects seems to be mostly at or below a 50% change from baseline. Notably, hormetic responses for integrative end points (such as cognitive function or behavior) characteristically involve a change of 30% to 60% over control. Considering this, the modest size of tDCS effects may be simply reflective of an intrinsically adaptive response to tDCS, rather than of ambiguity in the evidence for a reliable effect.

Current Flow Modeling (Marom Bikson, J. Patrick Reilly)

Although modern tDCS spans the past 15 years, the mathematical tools employed to predict current flow through biological tissues during electrical stimulation have been in development for decades.[163-168] Over the past 7 years, increasingly sophisticated models have been developed and applied to predict brain current during tDCS,[52,169-172] and these have been important to informing and creating new neurostimulation technologies and techniques.[55]

Despite the growing interest in theoretical modeling and the large number of currently completed and ongoing human trials, there have been relatively few attempts to validate models. Efforts thus far have included current flow validation through scalp measurements,[173] imaging,[174,175] surrogate suprathresholds waveforms,[176] and the use of in situ probes in phantom

skulls[177] and in live primates.[178] Such efforts have provided reasonable correlations of elicited motor reactions and EMG responses with existing computational models of peripheral neural stimulation.[179] However, retrospective and prospective models intended to explain and validate human trials of tDCS, providing only indirect evidence of model accuracy.[55,180-184]

Truly "gold standard" validation can be achieved through intracranial recording in humans (for example, from patients undergoing preoperative measurement for epilepsy treatment with acute implants or chronic deep brain stimulation implants) or through the use of brain probes in animal models. The design of a practical probe to explore the 3-dimensional electric field induced in the brain without materially affecting the field distribution requires particular attention.

Still, although precisely predicting electrical current flow patterns through the brain is of vital importance, it is equally crucial to develop a better understanding of how electric current applied to the brain generates distinct patterns of neural activity and influences cognitive processing and behavioral effects. This requires computational models that address and depict electrostimulation and effects of particular central neural sites and networks. However, development of a computational model for tDCS electrostimulation is especially challenging, considering that the electric field induced in the brain during tDCS is thought to be well below the threshold of excitation predicted by conventional neural stimulation models.

Transcranial DC electrostimulation model development should start with predicting which neural elements are activated by electrical stimulation,[185] including cell types (eg, excitatory pyramidal neurons, glia)[71,115] and the extent to which these are affected, as well as which—and to what extent—cellular structures are affected (eg, soma, dendrites, synaptic terminals, etc).[43,186] Extant models of tDCS differ from prior efforts in modeling electrical stimulation in an important way—tDCS is low-intensity, producing subthreshold polarization,[43,187] whereas most modeling efforts focused on suprathreshold stimulation that induced neuronal firing. To be sure, further validation of present models of tDCS current flow and the development of new models that span from current flow to induced changes at the cellular and network levels remain key challenges and opportunities to advance the science of tDCS.[188] We believe that a multidisciplinary approach, employing a number of neuroscientific and neurocognitive tools and techniques, is best suited to achieve these tasks.

Biomarkers and Imaging to Determine Mechanisms of tDCS (Vincent P. Clark, Emily Kappenman, Jessica Richardson)

Although some plausible hypotheses have been offered regarding the neurobiological mechanisms leading to the behavioral effects of brain stimulation methods such as tDCS, its effects are still uncertain in many respects. Biomarkers, including neuroimaging, offer the best way to identifying the effects of tDCS and infer its underlying mechanisms. It can also be used to guide the application of neurostimulation in order to enhance or fine-tune its effects and to examine issues related to its health effects and safety. A variety of different forms of neuroimaging currently exist today. These vary by the species tested (human vs animal), what type of information the imaging methods provide, and the range of spatial and temporal precision they are able to measure.

Invasive methods can be used typically on test animals or with humans who have severe neurological disorders requiring direct access to the brain for surgery. Although such work might help us to understand the direction and magnitude of current flow evoked by tDCS in the brain, much of the animal work has been performed using parameters that are substantially different (in terms of current density, duration, intra- vs extracranial, etc) from what humans are administered. Such differences make it difficult to translate these results to human tDCS mechanisms and may also be confounded by other differences, such as head size, skull thickness, and composition, and the effect of making holes in the skull to insert recording instruments.

Another basic distinction is between in vitro (in an artificial environment) and in vivo (in a living organism) neuroimaging methods. In vitro methods require that tissue is removed and studied outside the body. This is most often done using tissue from experimental animals. However, human tissue can also be obtained, either during surgery to excise diseased tissue or postmortem. In vitro testing allows for measurements of the activity of single neurons, even single ion channels within a single neuron, and allows for the precise control of the excised neuron's environment. In previous studies, it has been used to identify the effects of applied electrical fields on individual neurons and has given some evidence as to the possible mechanisms of whole brain effects of tDCS.[43,71,188,189] Although informative, removing neurons from their natural environment can alter their responses and difficulties in inferring effects of tDCS at the modular, areal, network, and regional levels from activity of single cells can lead to uncertainties in how activity at these different levels are related.

There are a variety of in vivo brain imaging methods, which can be categorized by their degree of invasiveness: (1) completely noninvasive, operating by recording energy produced naturally by the brain and passively moved out through the skull and scalp; (2) semi-invasive, operating by applying energy into the brain or substances into the bloodstream; and (3) fully invasive, passing recording devices through the scalp and skull directly into the brain. Neuroimaging methods can also be categorized by what physical characteristics of the brain are detected and recorded and what can be inferred from these measures. As we move from less to more invasive, these methods typically go from lower sensitivity and spatial precision to more so, but more invasive measures also typically involve greater potential for health-related issues and are consequently more risky to use.

Completely noninvasive methods include electroencephalography (EEG), which measures electrical activity produced by the nervous system, and magnetoencephalography (MEG), which measures magnetic activity. Both are direct measures of brain activity with submillisecond temporal resolution, making them

especially appealing tools to combine with brain stimulation, as they are able to follow changes in brain activity as they unfold over time.[190] This high temporal resolution provides unique information to supplement the complementary high spatial resolution information derived from other, more invasive techniques.

There have been a number of studies that use EEG in combination with tDCS, assessing changes in neural activity following administration of tDCS (sequential tDCS-EEG recordings) or assessing the changes in brain activity during tDCS (simultaneous tDCS-EEG recordings). Most studies to date have focused on sequential recordings, which avoid the potential problem of artifacts induced by simultaneous tDCS-EEG recordings (for more information, see Woods et al[191]). For example, EEG has been used to infer health effects of tDCS.[192] Electroencephalography and event-related signals derived from EEG (known as event-related potentials [ERPs]) have provided a window on the specific brain processes modulated by tDCS. For example, EEG recordings have been used to show that stimulation of the medial frontal cortex modulates ERP indices of error monitoring.[193] It has also been shown that tDCS applied in short bursts can modulate slow EEG activity (<3 Hz).[194] In some cases, EEG/ERP measures can be used to observe brain-related changes in the absence of overt corresponding changes in behavior, which make EEG/ERP measures particularly useful in assessing the subtle changes that may be induced by mild electrical brain stimulation.

Another potential use of EEG is as a method of determining the optimum location for the placement of tDCS electrodes. For example, EEG has been examined as a means of finding the optimum electrode location for tDCS administration in the treatment of tinnitus, wherein EEG measures were used to determine the precise location where gamma band activity was maximal in an individual as a target for placement of the cathodal electrode.[195] Although in this case the EEG-derived electrode placement provided no additional advantages over and above the traditional electrode placement in studies of tinnitus, this is a clear direction for future research. Electroencephalography has also been used with tACS to determine the individual alpha frequency to stimulate in order to modulate alpha power.[196]

There are also studies that have combined tDCS with MEG. Magnetoencephalography has been used to localize the effects of tDCS when applied over primary motor or sensory cortices.[197] Further, network activation and dynamics have been explored with MEG when tDCS is applied during rest[198] and during task.[199] Combining MEG with a powerful statistical approach (independent component analysis), tDCS-induced changes (polarity nonspecific) that outlasted the duration of the stimulation were observed in resting networks.[198] In Suntrup et al,[199] changes in brain oscillatory behavior (as indicated by increased event-related desynchronization power and spread) were observed during fast and challenged, but not simple, swallow tasks following anodal tDCS. Further, combining MEG with sensitive filtering (ie, beamforming) during the same experiment revealed the cortical swallowing network and important activation asymmetries in response to tDCS. Recently, MEG has also been combined with tACS.[61] Advances in filtering allowed for investigators to determine modulations of brain oscillations online during tACS administration for a wide range of frequencies, including that at which tACS was applied. Both EEG and MEG can also be used to measure network dynamics, which may be especially important in understanding how current flows through the brain beyond the portion of cortex directly underneath the electrodes. Electroencephalography- and MEG-measured network dynamics may also provide an especially useful means of determining the validity of current flow models of tDCS (discussed more above).

Moving higher in spatial resolution and lower in temporal resolution, a large variety of semi-invasive brain imaging methods exist. Two frequently used methods are magnetic resonance imaging (MRI) and positron emission tomography (PET). Magnetic resonance imaging applies a combination of static and fluctuating magnetic fields with radiofrequencies designed to image the concentration and local environments of atomic nuclei.[200] The most common nuclei imaged by MRI are hydrogen protons contained in water molecules. Depending on the timing, frequency, and strength of applied magnetic fields and radio waves, MRI can be used to obtain gross structural MRI (sMRI), fine structural (diffusion along white matter pathways using diffusion tensor imaging [DTI] or diffusion kurtosis imaging [DKI]), spectroscopic (magnetic resonance spectroscopy [MRS]), and functional MRI (fMRI) images. More invasive forms of sMRI and fMRI exist that use injected gadolinium or other exogenous agents to alter local magnetic field strengths in ways that help to enhance contrast in images. In contrast to MRI, PET uses injection or inhalation of radioactive tracers, which can be detected inside the body and used to examine a variety of chemical or metabolic pathways depending on the exact tracer substance used.[201] Examples of how these neuroimaging methods have been applied to tDCS are summarized below.

Structural MRI can reveal the brain's structure to millimeter resolution, making this an ideal tool for developing models of current flow and electrode placement[202] and also for coupling with other technologies to localize the effects of tDCS. Advanced techniques such as DTI and DKI can even isolate specific tissues (eg, white matter tracts) for characterization and can be used to measure structural changes in the brain that may occur after tDCS exposure, particularly extended use or sessions. Incorporating DTI into electric field modeling will be important when planning electrode placement for individuals with TBI, where often damage in this population can only be visualized with DTI and not with high resolution T1 or T2 structural images.

Structural MRI combined with finite element modeling has also been used to estimate individual differences in current flow with tDCS. Laakso et al[203] developed head models for 24 subjects and examined individual variability in current intensities in the brain. They found that variations in the electric fields of the hand motor cortex had a standard deviation (SD) of approximately 20% of the mean and that cerebrospinal fluid (CSF) thickness was the primary factor influencing an individual's electric field, explaining 50% of the

interindividual variability, with a thicker layer of CSF decreasing field strength at the brain surface. The next step in such work might be to compare the magnitude of tDCS effects on behavior with estimates of field strength and to determine whether field strength in specific areas of the cortex is an important predictor of tDCS effects. The long-term effects of tDCS on brain anatomy has been studied by Zheng and Schlaug,[204] who found that daily active tDCS over motor cortex, coupled with physical/occupational therapy in recovering patients with stroke, altered FA in the cortico-tegmental-spinal tract compared to sham. The change in FA correlated with improved scores of motor function, suggesting that white matter structural changes may be involved in the long-term behavioral effects of repeated tDCS.

A variety of published studies have used fMRI or PET to examine changes in brain activity associated with tDCS. As 1 example, Brunelin et al[205] first showed that a multiday tDCS protocol could be used to reduce patients' reports of auditory and verbal hallucinations. Based on this work, Mondino et al[206] showed using resting-state fMRI that the same protocol reduced connectivity of the left temporoparietal junction and the left anterior insula, which was correlated with reduced hallucinations. As another example, Wang et al[207] found that tDCS over the portion of somatosensory cortex representing the foot increased BOLD fMRI responses in that area in response to foot stimulation. Other studies have used fMRI to plan application of tDCS. Matsushita et al[208] used prior fMRI studies of pitch discrimination to identify regions involved in this perceptual process and were able to reduce pitch discriminability by stimulation of this region.

A series of studies[134,135,209] used BOLD fMRI to examine the relationship between brain regions involved in learning to detect target objects placed in complex images and the effects of tDCS applied to these functional regions. Overall, fMRI predicted the effects of both anodal and cathodal tDCS, suggesting that fMRI may provide a good guide for determining optimal placements for tDCS. This general result needs to be confirmed using other cognitive tasks and other forms of neuroimaging to evaluate the sensitivity and specificity of this relationship. Few arterial spin labeling (ASL) fMRI studies have been conducted, with mixed results that are likely to be at least partially attributable to differences in stimulation protocols. The investigations so far have focused on polarity-specific effects and aftereffects of tDCS on brain activation, as measured by increased or decreased cerebral blood flow (CBF), and on the effects of tDCS on cortical network activity,[210-213] which used fMRI to show changes in the stimulated region concurrently with tDCS. These authors applied anodal tDCS over the hand region of the precentral gyrus and showed brain activity changes in M1, supplementary motor area, and the contralateral parietal region.

Magnetic resonance spectroscopy is readily combined with sMRI so that the concentration of various chemicals (metabolites) within a selected voxel or brain region can be determined. A small number of MRS studies with tDCS have been performed to examine the neurochemical effects of tDCS. Rango et al[214] found an increase in myoinositol with tDCS. Stagg et al[215] demonstrated that anodal tDCS leads to statistically significant reductions in GABA concentration relative to sham conditions, whereas cathodal stimulation is associated with reduced glutamatergic neuronal activity with a highly correlated reduction in GABA. Clark et al[145] found that anodal tDCS produces a localized increase in glutamate and glutamine and also in NAA under the stimulating electrode but not in the opposite hemisphere. These changes were also correlated with changes in within-network connectivity for brain networks located nearby the stimulating electrode.[146] This suggests that anodal tDCS produces changes in excitatory neurotransmission locally, which affects brain activity more broadly in turn.

A few studies have examined the effects of tDCS on PET-derived images. One of the first and currently most highly cited is by Lang et al,[159] who found a complicated pattern of increased and decreased activity using 15O PET with left M1 versus right frontopolar tDCS. In another example, Paquette et al[216] found that cathodal tDCS did not affect total CBF at rest but did reduce the change in CBF related to performing a motor task and concluded that there is an interaction of cathodal tDCS with activation-induced changes in regional cerebral blood flow (rCBF), rather than an effect on resting or activated rCBF itself. DosSantos et al[217] used [^{11}C] carfentanil to image μ-opioid receptor availability during tDCS over motor cortex in 1 patient with chronic temporomandibular joint (TMJ) pain, which has been found to reduce pain perception. They found reduced binding, suggesting an increase in opioid release due to tDCS. Another PET study of tDCS effects on pain[218] used ^{18}F-fluorodeoxyglucose, which images metabolic activity. They found increased metabolism in the medulla, subgenual anterior cingulate cortex, and insula and decreased metabolism in the left DLPFC for active tDCS compared to sham, which may help to explain some of the analgesic effects of tDCS.

In conclusion, there are a large variety of neuroimaging methods that can be applied to the study of the effects and mechanisms of tDCS. Recent studies have shown a variety of effects of tDCS, but much work remains. Through the careful and intelligent combination of neuroimaging with neurostimulation, much can be learned about the mechanisms and optimization of tDCS.

The Trajectory and Tasks of Research in TES and Its Translation to Clinical Practice (James Giordano)

Clearly, there is evidence to support the validity and viability of various types of tES—inclusive of tDCS—to elicit neurocognitive effects that could be of value to medical and occupational settings and communities. Claims that extant results are inconclusive or even indicative of a lack of effect(s) and/or of effectiveness of tDCS can be countered by more stringent analysis of findings, paying particular attention and reference to contexts of experimentation, use, conditions of test subjects, and ecological variables.[50,141,143]

Given these remaining unknowns, and increasing interest in—if not demand for—neuromodulatory approaches by both factions of the medical community and the general public, there is a defensibly ethical imperative for ongoing research, as well as prudent translational uses in clinical and perhaps other (eg, occupational) settings. Thus, studies of efficacy and mechanisms are certainly of benefit, but effectiveness research is also critical. Herein lies a caveat—the ethical probity of any such translation into clinical, occupational, and public use demands efforts to maximize safety, which involves preparation, both (a) in advance of use to determine parameters and protocols for best benefit and (b) during/after use to address and mitigate any and all adverse or deleterious effects.[219-223]

Findings from experimental and ''real-world'' applications of tES are important to develop and sustain a more meaningful evidence base to guide the ways that these techniques and technologies can and should be employed and those settings and situations in which they should not. In the main, it will be important to weigh and balance the potential benefits and harms of commission (ie, engaging tES) and omission (ie, not engaging/using tES).[219,220,224,225] Information from the biomedical research, direct-to-consumer, and do-it-yourself communities suggests and supports broader use, as well as the utility and effectiveness of tES. Some of this information may be anecdotal and derived from case and/or case series reports, yet it is nevertheless vital to document and follow. Essential to such efforts is an accurate, aggregated database that details methods (eg, device, montage(s), dosimetry, setting, etc) and effects (eg, main effects/outcomes on specific parameters of dependent variable(s) evaluated, collateral effects, etc), so as to more precisely determine what works, in whom, to what end, and under what contexts and circumstances. This would afford a repository for harvesting raw data, data integration, and exchange. Further, wide(r) data access and use would enable large- and small-scale meta-analyses and systematic review(s), in order to maximize utility and optimize results.[226,227] Toward this end, it will be crucial to evaluate the ways that current, revised, and newly proposed frameworks and tools could be used, modified, established, and maintained, and identify, address, and attempt to resolve the neuroethico-legal issues and problems that such a database—and the use or nonuse of tES in specific circumstances and under particular conditions—may incur. Our group remains dedicated to these tasks, opportunities, and challenges.

Authors' Note

Proceedings of the Air Force Research Planning Meeting: This paper presents statements by subject matter experts and opinion leaders in neuromodulation and related disciplines, which are intended to summarize the state-of-the-science in specific domains, and where applicable, suggest a road map toward identifying and addressing key research and deployment challenges and opportunities. This report contains a series of sections that were written by the individual(s) listed within each section. All sections have been integrated into a single document that intends neither to yield a consensus view nor to represent an endorsement by the authors as a whole or the Air Force Office of Scientific Research of any single statement, opinion, or subsection.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CUNY has patents on brain stimulation with Bikson as an inventor. Bikson has equity in Soterix Medical Inc. Nitsche is on the advisory board of neuroelectrics—producing DC stimulators.

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