

SPECIAL ISSUE

Stimulation Technologies: “New” Trends in “Old” Techniques

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Optimal functioning of the brain and mind is essential for good mental health and well-being. Unfortunately, disruptions in specific brain region function may arise for a variety of reasons, which include adverse genetic predispositions, poor nutrition, illness and cerebral accidents, developmental hormonal shifts, and negative life events resulting in overload and stress reactions. Fortunately, there are low-cost, easy-to-use, and effective electronic brain-stimulating technologies available today. These stimulation technologies include audiovisual entrainment (AVE) devices (e.g., light and sound machines), as well as electrostimulation technologies such as cranio-electro stimulation and transcranial direct current stimulation. The instruments are all designed to aid individuals with modulating their own cortical arousal levels, whether to regain lost functionality or to enhance outcomes such as improved social interactions, athletic performance, mathematical problem-solving, or creating new art and music. This article reviews a range of current techniques used for stimulating and modulating brain regions for positive gain.

Introduction

Stimulation technologies (STs) span a wide variety of techniques, some of which require instruments. In the broadest use of the term, there are many activities that engage the brain that could be considered an ST. For example, many physically challenging activities such as biking, climbing, skiing, and diving, as well as cognitively challenging activities such as playing chess, writing, storytelling, solving math problems, and playing music or card games, video games, and many more, may all be said to stimulate the brain and encourage a sense of well-being (Marques-Alexio et al., 2015; Meeusen, 2014; Protzner et al., in press).

This article focuses on a particular set of devices designed to stimulate brain activity more directly. For example, audiovisual entrainment (AVE) or stimulation techniques

have been shown to increase activity in distinct brain circuits preferentially using rhythmic entrainment (Trost et al., 2014), to reduce insomnia (Tang, Riegel, McCurry & Vitiello, 2015), or to improve attention (Treviño et al., 2014). Additional STs include low-level cranio-electro stimulation (CES) techniques that have been shown to improve symptoms of fibromyalgia through stimulation of the basal ganglia (Anderson, Kebaish, Lewis, & Taylor, 2014; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2009), or symptoms of Tourette’s syndrome (Qiao, Weng, Wang, Long, & Wang, 2015). Another approach to brain function modulation includes transcranial stimulation. For example, transcranial direct current stimulation (tDCS) techniques have been shown to influence the resting states of neural networks (M. D. Fox et al., 2014). A useful overview of neuro-enhancement techniques using STs is also provided by Clark and Parasuraman (2014).

This article also provides a host of historical references spanning several decades of evidence that describe and review STs that are compact and low-cost. All of the protocols and procedures that use the equipment are designed to increase or decrease brain activity for a beneficial outcome. These brain stimulation and modulation approaches can be achieved using a few categories of devices:

1. light and sound stimulation devices, most commonly referred to as audiovisual stimulation (AVS) or AVE devices, in which sound (e.g., isochronic beats) and light (pulsed or flickering light-emitting diodes) are presented at specific frequencies to guide various cortical regions into desired activation patterns;
2. CES devices, in which a small pulsed current (up to 5 mA) flows through electrodes placed on the mastoid bones or ear lobes to stimulate brain regions around the temporal lobes and the brain stem (CES is sometimes

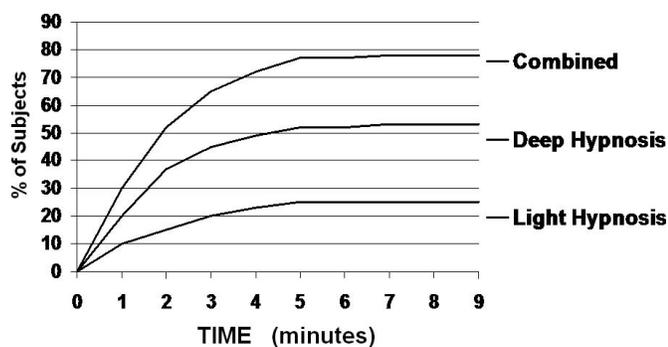


Figure 1. Photic stimulation induction of hypnotic trance (Kroger & Schneider, 1959).

referred to as transcranial pulsed current stimulation); and

- transcranial electrical stimulation devices, in which a small current (up to 2 mA) flows through electrodes placed on specific sites on the head for stimulating various brain regions. Transcranial stimulation includes tDCS, in which an anode or cathode may be used to augment or inhibit brain function. Some studies have also explored transcranial AC stimulation, in which an electrical stimulus of a given frequency is used to drive brain waves up or down, as well as transcranial random-noise stimulation, in which the electrical stimulation occurs in the range of actual neuronal firing (150–300 Hz).

For reference, there is another ST that will not be reviewed in this article, specifically transcranial magnetic stimulation devices, in which electromagnetic coils are pulsed at various levels (e.g., micro tesla through tesla range). The resulting electromagnetic field stimulates various structures of the brain. For the remainder of this article, three categories of technologies are reviewed: AVE, CES, and tDCS.

Audiovisual Entrainment

AVE is a technique in which lights flash into the eyes while tones pulse into the ears. The frequency of the lights and tones is in the brain wave frequency range, typically from 1 to 40 Hz. AVE technologies are to be avoided in those with photosensitive epilepsy, where flashing lights of certain frequencies may trigger a seizure (Erba, 2001; Trenité, Guerrini, Binnie, & Genton, 2001). AVE is one of the most intriguing STs because AVE devices have been shown to influence by varying degrees brain activity associated with (a) dissociation/hypnotic states, (b) autonomic nervous system calming/meditative states, (c) increased cerebral

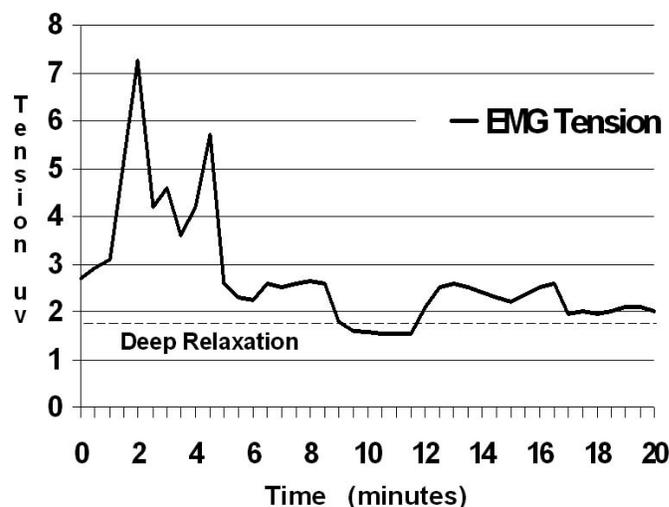


Figure 2. Forearm EMG levels during AVE (Hawes, 2000).

blood flow (CBF), and (d) increased neurotransmitter activity.

Dissociation/hypnotic induction. Several studies have been completed since the 1950s on hypnotic induction and dissociation (Leonard, Telch, & Harrington, 1999, 2000; Lewerenz, 1963; Margolis, 1966; Sadove, 1963; Walter, 1956) and altered states of consciousness (Glicksohn, 1986; Hear, 1971; Lipowsky, 1975). The first study on dissociation induced via entrainment involved hypnotic induction, which found that photic stimulation at alpha frequencies could easily put subjects into hypnotic trances (Kroger & Schneider, 1959). Figure 1 shows the results of Kroger and Schneider's study in which nearly 80% of the participants in the study were in a hypnotic trance within 6 min of photic entrainment.

Autonomic calming. Assisting clients with trauma histories to dissociate (in a constructive and meditative way), during the course of treatment, is important. For example, McConnel, Froeliger, Garland, Ives, and Sforzo (2014) demonstrated that auditory “driving” of nervous system reactivity using binaural beats resulted in increased parasympathetic nervous system calming. These changes in autonomic nervous system reactivity reflect a return to homeostasis or restabilization, hence the term *dissociation and restabilization* (Siever, 2003). Although brain wave activity changes are typically associated with alpha and theta stimulation techniques, autonomic calming and enhanced meditative states have been observed during dual frequency stimulation such as beta/SMR training protocols (e.g., left-sided stimulation of 20 Hz and right-sided

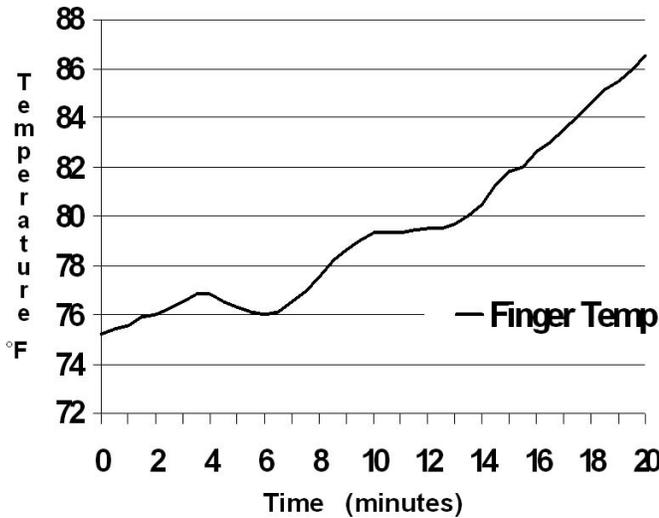


Figure 3. Peripheral temperature levels during AVE (Hawes, 2000).

stimulation of 14 Hz; Leach, 2014; Regaçone et al., 2014). Other examples of the calming effects of AVE are shown in the following figures. For example, Figure 2 by Hawes (2000) shows a typical reduction in forearm SEMG, and Figure 3 by Hawes (2000) shows a typical increase in finger temperature during AVE. Notice that restabilization begins after about 6 min of AVE, when the user begins dissociating and the autonomic nervous system calms down.

Cerebral blood flow (CBF). CBF is essential for good mental health and function. Single photon emission computed tomography and functional magnetic resonance imaging of CBF show that hypoperfusion of CBF is associated with many forms of mental disorders (Amen, 1998). Decreases in CBF in frontal brain regions have been associated with disorders that include anxiety, depression, attentional and

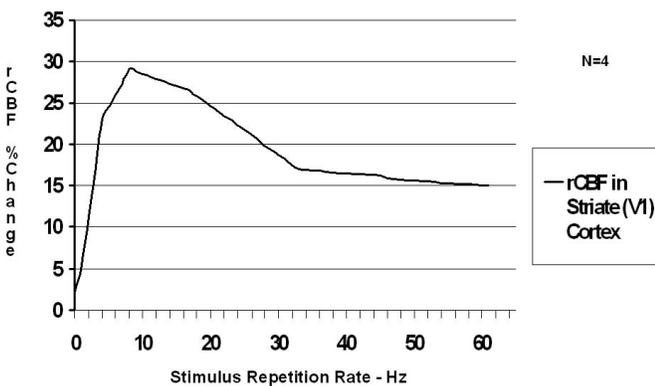


Figure 4. CBF at various photic entrainment repetition rates (P. Fox & Raichle, 1985).

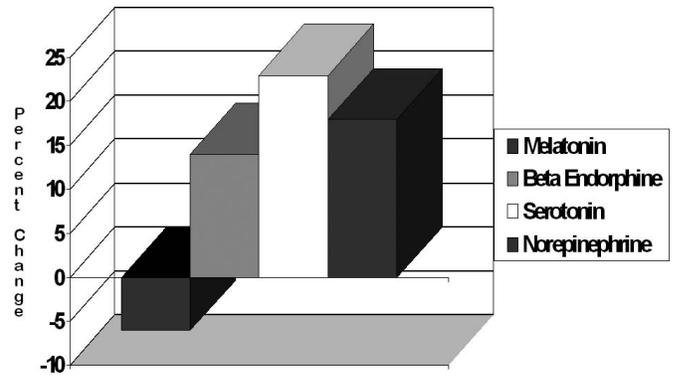


Figure 5. Neurotransmitter levels following AVE (Shealy et al., 1989).

behavior disorders, and impaired cognitive function (Amen, 1998). Some of the purported beneficial effects of AVE have been attributed to increases in frontal region CBF (cf. P. Fox & Raichle, 1985; P. Fox, Raichle, Mintun, & Dence, 1988; Sappey-Mariniier et al., 1992). For example, Figure 4 shows an increase of 28% in CBF within the striate cortex, a primary visual processing area within the occiput. As an interesting note, maximal increases in CBF has been shown to occur with photic stimulation at 7.8 Hz, which is known as the “Schumann resonance” of the earth (Collura & Siever, 2009, p. 214).

Increased neurotransmitter activity. There is evidence that blood serum levels of serotonin, endorphin, and melatonin rise considerably following 10-Hz, white-light AVE (Shealy et al., 1989). Increases in endorphins reflect increased relaxation, whereas increased norepinephrine along with a reduction in winter daytime levels of melatonin, indicate increased alertness (Figure 5).

AVE effects are primarily associated with frontal brain regions and are near the vertex (Frederick, Lubar, Rasey, Brim, & Blackburn, 1999; Siever, 2002). For example, Figure 6 is a quantitative electro-encephalograph (QEEG), or “brain map” from the Serman-Kaiser Imaging Labs database, in 1-Hz bins showing the frequency distribution of AVE at 8 Hz. The area within the circle at 8 Hz shows maximal effects of AVE in central, frontal, and parietal regions (at 10 uv in this case) as referenced with the oval area on the legend. It is through associated influences on frontal brain regions that AVE has been shown effective in reducing depression, anxiety, and attentional disorders. For the more advanced reader, a harmonic is also present at 16 Hz (the circled image), which is typical of semisine wave (part sine/part square wave) stimulation.

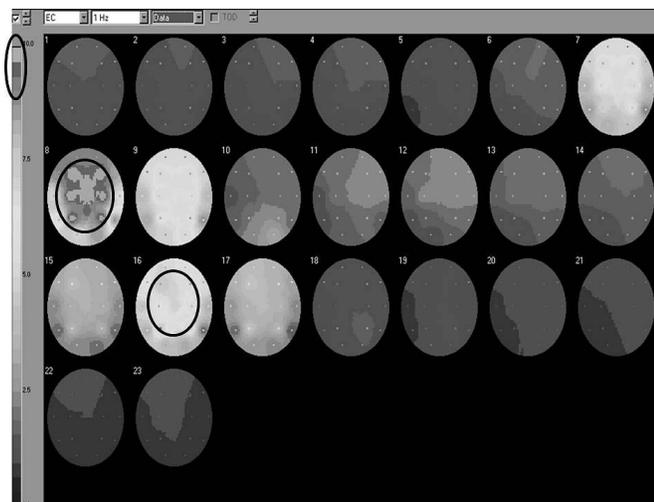


Figure 6. Brain map in 1-Hz bins, during 8 Hz AVE (Stermán-Kaiser Imaging Labs—eyes closed).

Over the past several decades, AVE has been associated with several types of beneficial outcomes in clinical studies (e.g., Berg & Siever, 2009; Budzynski, Budzynski, & Tang, 2007; Budzynski, Jordy, Budzynski, Tang, & Claypoole, 1999; Budzynski & Tang, 1998; Carter & Russell, 1993; Criswell, 2014; Donker, Njio, Van Leewan, & Wieneke, 1978; Gagnon & Boersma, 1992; Joyce & Siever, 2000; Manns, Miralles, & Adrian, 1981; Micheletti, 1999; Morse & Chow, 1993; Regan, 1966; Russell, 1996; Ruuskanen-Uoti & Salmi, 1994; Siever, 2002, 2003; Thomas & Siever, 1989; Townsend, 1973; Trudeau, 1999; Van der Tweel & Lunel, 1965; Wolitzky-Taylor & Telch, 2010; Wuchrur, 2009). Because there is not space in this brief review article to describe all of the studies cited, Table 1 lists a variety of clinical conditions, along with a number of studies (and the size of the population), as well as the type of demographic.

One mechanism of action attributed to AVE, and to some degree all STs, is related to frequency driving of brainwave activity (McConnel et al., 2014). By definition,

Table 1. Clinical studies involving audiovisual entrainment

Condition	Studies (N)	Demographic
Attention Deficit Disorder	4 (359)	School children
Academic performance in college students	3 (134)	College students
Reduced worry/anxiety in college students	3 (163)	College students
Drug rehabilitation	1 (44)	General population
Depression and anxiety	3 (93)	General population
Improved cognitive performance in seniors	1 (40)	From seniors' homes
Reduced falling and depression in seniors	1 (80)	From seniors' homes
Memory in seniors	1 (40)	Seniors: Drop in
Dental (during dental procedures)	3 (>50)	Patients
Temporo Mandibular Dysfunction	3 (76)	General population
Seasonal Affective Disorder	1 (74)	General population
Headache (migraine and tension)	2 (35)	General population
Neurophysiology	15 (xx)	General population
Heart rate variability and hypertension	5 (148)	General population
Hypnosis/dissociation/meditation	10 (>2,000)	General population
Pain and fibromyalgia	5 (178)	General population
Insomnia	1 (10)	General population
Post Traumatic Stress Disorder	1 (15) ~600 cases	Public, military, police
Literature reviews	5	Diverse population
Premenstrual Syndrome	2 (23)	General population

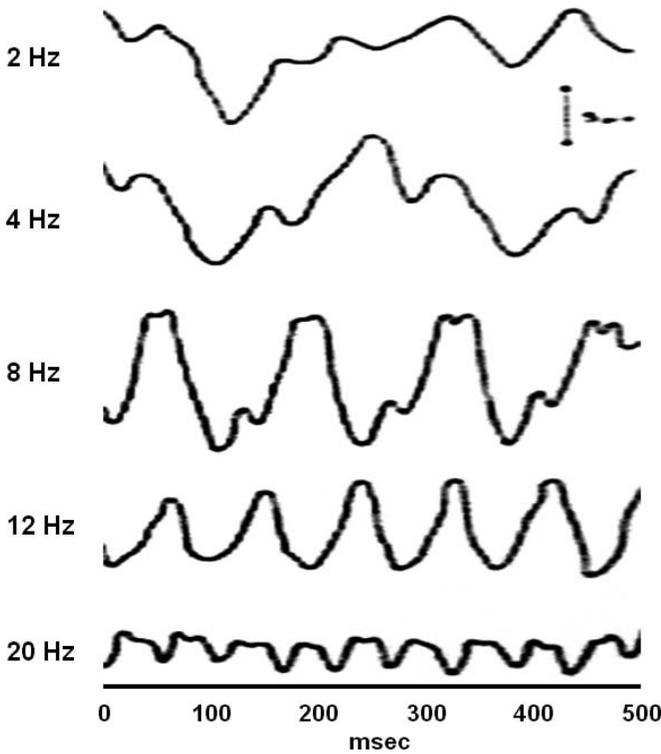


Figure 7. EEG showing photic entrainment (Kinney et al., 1973).

entrainment occurs when a bodily rhythm reflects the rhythm of the stimuli to which it is exposed. For example, brain waves observed via EEG reflect the dominant brain wave frequency duplicating the frequency of an auditory, visual, or tactile stimuli (Siever, 2002). Photic driving of brain waves was first discovered by Adrian and Matthews back in 1934, whereas auditory entrainment was first demonstrated by Chatrian, Petersen, and Lazarte in 1959. Photic entrainment occurs best near one’s own natural alpha frequency (Kinney, McKay, Mensch, & Luria, 1973; Toman, 1941). Figure 7 shows photic entrainment at a variety of frequencies.

Cranio-Electro Stimulation

CES is primarily a brain-calming technique with neurotransmitter effects like those of AVE. The CES technologies deliver small pulses of electrical current (up to 5 ma) through the brain. CES is typically applied bilaterally across the cranium via the placement of two small electrodes on the ear lobes, the mastoid processes, or occasionally the temporal lobes. CES devices typically employ direct current (DC) or alternating currents (AC) in audio frequencies typically from 0.5 to 100 Hz, and one device uses 15 KHz, modulated with 15 Hz and 500 Hz. Whereas AVE technologies may be contraindicated for individual with certain photo sensitivities, given its electrical nature, CES is not to be used on those who have a pacemaker or other implanted life-preserving bioelectric appliances (Hallett, Brewster, & Rasmussen, 2001; Southworth, 1999).

There are various theories as to how CES affects various brain regions. For example, Figure 8 shows high-resolution modeling depicting several brain regions (e.g., brain stem, the limbic system, the reticular activating system, and/or the hypothalamus) when using electrodes placed on the ears (Datta, Dmochowski, Guleyupoglu, Bikson, & Fregni, 2013). The modeling suggests some of the current (electron flow) path went through the brain stem, in particular the medulla, plus the posterior aspect of the hypothalamus (circled areas). Whether the release of neurotransmitters is triggered by AVE or CES techniques, many brain regions stimulated by AVE, CES, and tDCS techniques are correlated with release of the neurotransmitters such as serotonin, norepinephrine, dopamine, and acetylcholine. For example, neurotransmitters produced within the brain stem have been shown to be modulated

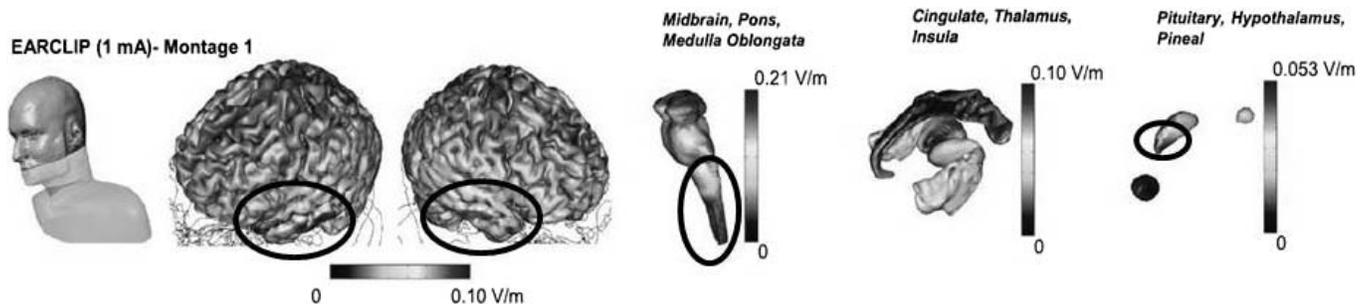


Figure 8. Peak electric field distribution with CES from 3 to 100 Hz (Datta et al., 2013).

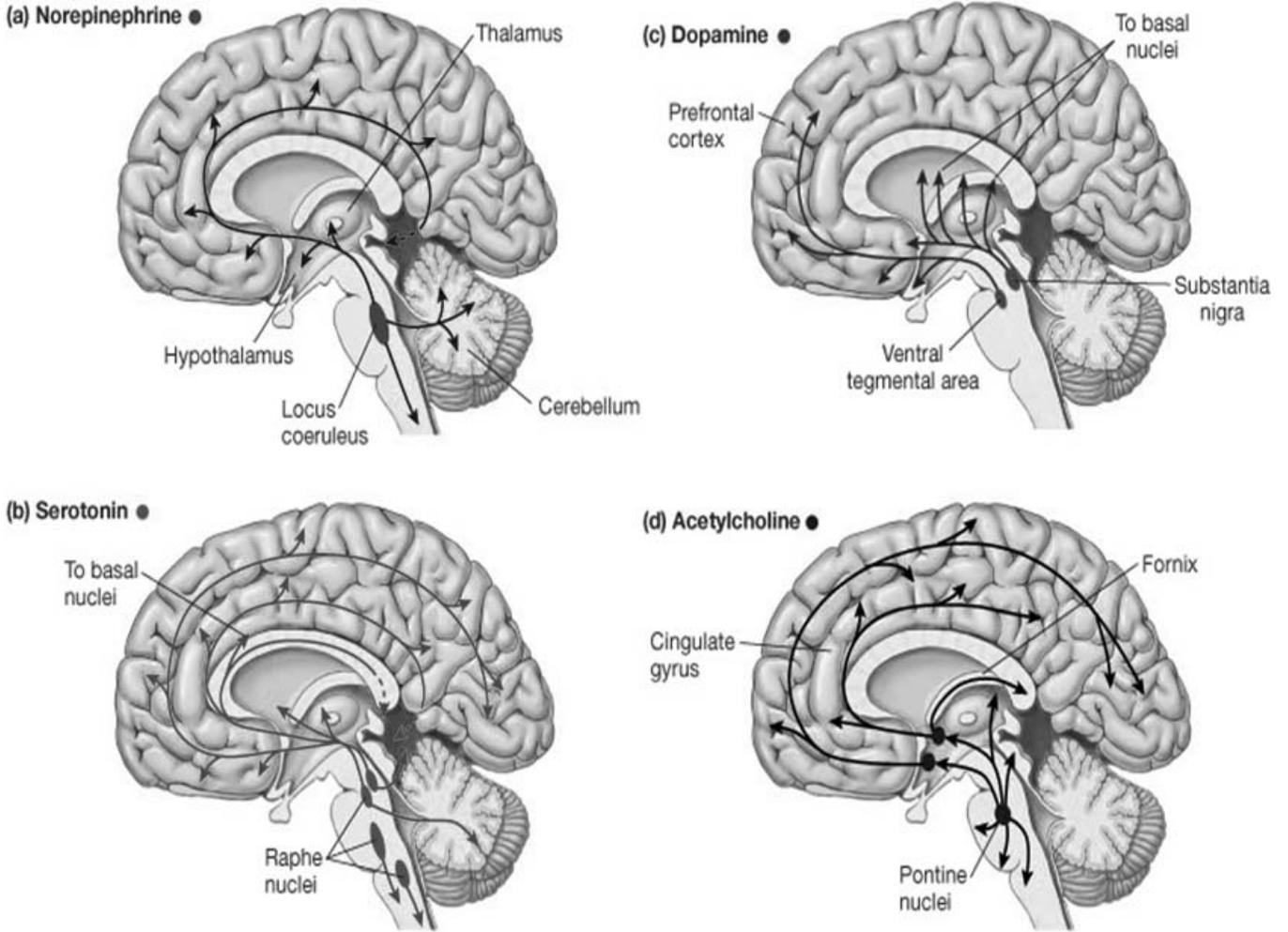


Figure 9. Neurotransmitter pathways originating from the brain stem (Silverthorn, 2003).

by the hypothalamus as shown by Silverthorn (2003), in Figure 9.

Shealy, Cady, Culver-Veehoff, Cox, and Liss (1988) compared neurotransmitter levels from blood-serum measures with that of cerebral spinal fluid (CSF) following

CES exposure. The study was meant to prove that CSF measurements were considerably more accurate than blood serum measures. But in the process, they found that average increases of beta endorphin and serotonin

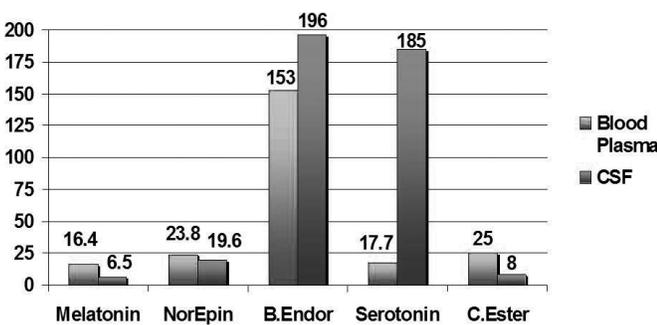


Figure 10. Blood serum versus CSF measures of neurotransmitters following CES (Shealy et al., 1988). B.Endor = beta-endorphin; C.Ester = cholinesterase.

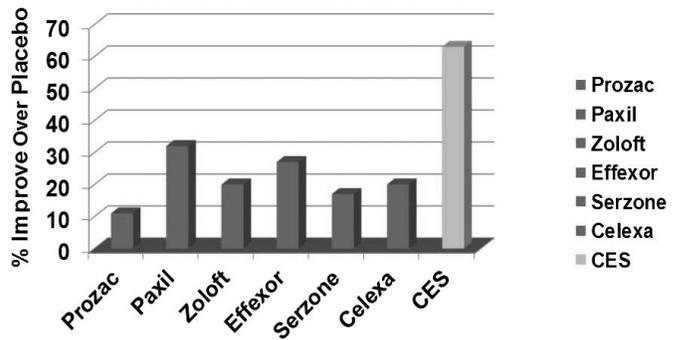


Figure 11. Medication treatments versus CES for treating depression (Gilula & Kirsch, 2005).

Table 2. Significant studies of cranio-electro stimulation by 2012 (adapted from Ray Smith, 2006)

Syndrome	Total studies	Double blind	Single blind	Other	Total participants	Average improvement (effect size)
Insomnia	18	7	3	8	648	67%
Depression	18	7	2	9	853	47%
Anxiety	38	21	1	16	1,495	58%
Drug abstinence	15	7	4	4	535	60%
Cognitive dysfunction	13	3	4	6	648	44%

production following CES were quite dramatic, as shown in Figure 10.

Drug Use versus CES for the Treatment of Depression

Because depletions in serotonin, norepinephrine, and dopamine are well documented with major depressive disorder (Nutt, 2008), using CES to influence increased neurotrans-

mitter activity with depressive clients may be beneficial with no pharmacological side effects. For example, a meta-analysis by Gilula and Kirsch (2005) of 290 depressives showed a direct comparison of CES against various depression medications. Figure 11 shows the treatment-effect improvement in depression over placebo obtained from freedom-of-information data as provided to the Food and Drug Administration (FDA) from pharmaceutical companies when seeking FDA approval. The CES data came from eight studies submitted to the FDA from Electromedical Products International, Inc., to reclassify CES from Class III to Class II for the treatment of depression, anxiety, and insomnia. The CES studies had no reported negative side effects, whereas the drug studies indicated side effects ranging from interruption of liver metabolism to reactions with other medications and an increase in thoughts and behaviors related to suicide ideation.

CES Clinical Studies

There have been approximately 200 clinical studies using CES, spanning 50 years using over 25 devices (Kirsch, 2002). For example, Smith (2006) completed an extensive analysis of the more credible studies of CES and cross-referenced them into effect size, a unique type of statistical analysis, so they could be compared with other treatment modalities, as shown in Table 2.

Transcranial DC Stimulation

One of the recent neuromodulation techniques is tDCS. Although still considered investigational by the FDA, and officially limited to research use within the United States, tDCS has shown itself to be effective in influencing a wide variety of clinical symptoms in a variety of studies as shown in Table 3. It is an easy-to-use technology with only some mild undesirable side effects reported. Given its electrical nature, tDCS is not to be used on those who have

Table 3. tDCS studies by category

Symptom category	N
Addiction	7
Behavior	20
Depression/bipolar/anxiety	31
Cognition	58
Language (aphasia, speech)	57
Memory (episodic, semantic, name recall)	27
Migraine	6
Motor and motor learning	80
Neurotransmitters	18
Pain	43
Parkinson's (memory)	3
Physiology (EEG, brain function, CBF)	52
Psychiatric (schizophrenia, OCD, anorexia)	11
Sensory	12
Somatosensory and tactile sensitivity	15
Animal studies	15
Literature reviews	46

Note. EEG = electro-encephalograph; CBF = cerebral blood flow; OCD = Obsessive Compulsive Disorder.

a pacemaker or other implanted life-preserving bioelectric appliances. Technically, tDCS is easier to use than other neuro-stimulation techniques such as rTMS, AVE, or neurofeedback.

Technical Aspects of tDCS

Because tDCS is still considered an investigational technology by the FDA, this review includes a more detailed description of the purported mechanisms of tDCS effects. Current theory suggests that positive electrode (anode) stimulation depolarizes the local neurons by 5 to 10 mV from their typical resting potential of 65 to 55 mV, which in turn will require less dendritic input to fire (depolarize) the neuron. Negative electrode (cathode) stimulation hyperpolarizes the neuron slightly and it will require increased dendritic input to fire it (Nitsche & Paulus, 2000, 2001). Stagg et al. (2009) used magnetic resonance spectroscopy to observe that anodal stimulation decreases levels of local gamma amino butyric acid, an inhibiting neuromodulator, thus increasing neuronal activity, whereas cathodal stimulation primarily decreased local glutamate (an excitatory neuromodulator) levels, thus reducing neuronal activity. It has also been shown that anodal stimulation increases CBF (Zheng, Alsop, & Schlaug, 2011), as well as beta and gamma brain wave activity (Keeser et al., 2011). Cathodal stimulation reduces CBF while increasing delta and theta brain wave activity. Recent observations suggest that brain activity (as measured with functional magnetic resonance imaging or PET) under the anode is enhanced by roughly 20% to 40% when the current density (concentration of amperage under the electrode) exceeds $40 \mu\text{A}/\text{cm}^2$ ($260 \mu\text{A}/\text{inch}^2$; Siever, 2013). The cathode reduces brain function under the electrode site by 10% to 30% at the forementioned current density. Anodal stimulation is the most common form of tDCS because most applications require enhanced brain function (Siever, 2013).

The brain-stimulating electrode is termed the *active* electrode, whereas the circuit-completing electrode, which may be active or inactive, is called the *reference* electrode. In most of the studies, the reference has been placed over the contralateral orbit (above the left or right eye). To date, most studies have neglected to look at the inhibiting or boosting effects that the reference electrode might have on the brain regions where it is placed; however, a few studies, and in particular a study by Nitsche et al. (2007), showed that it is better to have a small stimulating electrode and large reference electrode. The suggestion is that the current density is high under the treatment electrode and low under the reference electrode. The arrangement of differing

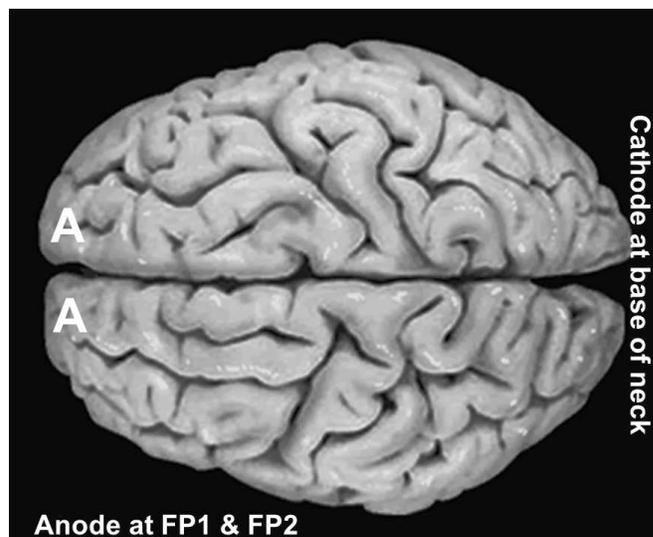


Figure 12. Improving attention and the “Mendonca method” for reducing pain (Mendonca et al., 2011).

electrode sizes allows the reference electrode to be placed almost anywhere over the scalp without it affecting brain function beneath it.

Most studies have used stimulation at 1 mA of current through $7 \times 7 \text{ cm}$ (49 cm^2) electrodes; however, some studies have used smaller surface area electrodes (e.g., a 1-in. square electrode is $2.54 \times 2.54 \text{ cm} = 6.45 \text{ cm}^2$). Fregni et al. (2008) suggested using a shoulder for the reference placement, except possibly for treating depression, where the active electrode (anode) should be placed over the dorsolateral prefrontal cortex (F3 on the 10–20 electrode montage) and the cathode over F4.

QEEG to assist with electrode placement

One important method to help determine electrode polarity and placement is to use a 19-channel QEEG and a normative database to assess where brain activity may be too little or excessive. If identifying a brain region shows delta, theta, or alpha brain wave frequencies that are excessive, then it is suggested to use tDCS anodal stimulation. When beta brainwave activity is high in relation to the slower bands, then consider cathodal stimulation.

The Figures shown demonstrate the diversity of tDCS. For example, Figure 12 shows the “Mendonca method” (Mendonca et al., 2011) for reducing pain (as well as boosting attention). Many studies have been completed for enhancing function of the left dorsal-lateral prefrontal cortex, or F3, with anodal stimulation and various cathode

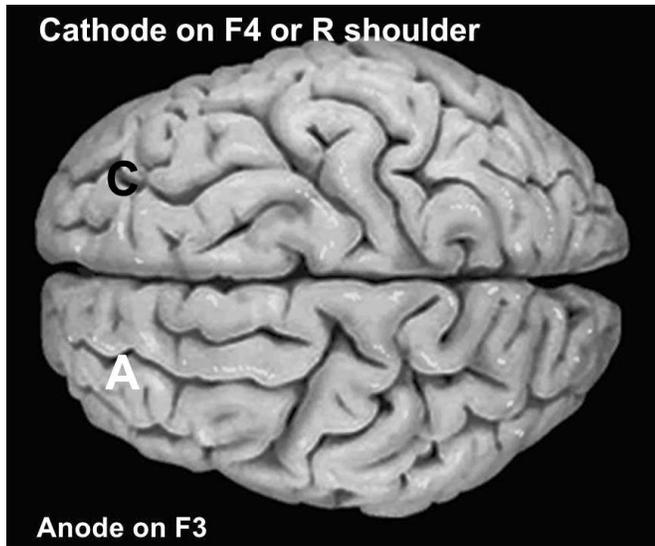


Figure 13. Treating depression, addictions, and cravings while improving planning ability.

configurations such as placement at F4, the right orbit, or right shoulder (F3 anode/F4 cathode montage shown in Figure 13) for treating depression (Fregni et al., 2006; Martin et al., 2011), addiction (Boggio et al., 2008), and cognitive and organizational skills (Kadosh, 2013). Figure 14 depicts a study of insightfulness during a cognitive game (Chi & Snider, 2011) in which this montage increased insightfulness needed to solve the puzzles in the games. Broca’s and Wernicke’s aphasias are common and debilitating outcomes of stroke. Figure 15 shows an effective

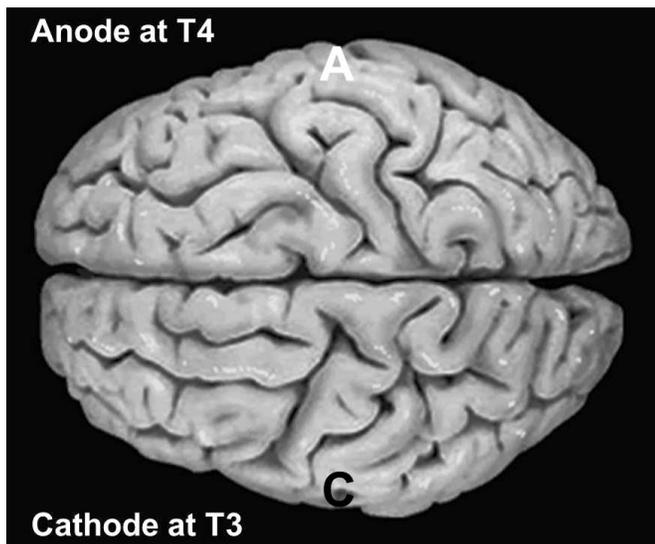


Figure 14. Improving insightfulness by improving global perception (Chi & Snider, 2011).

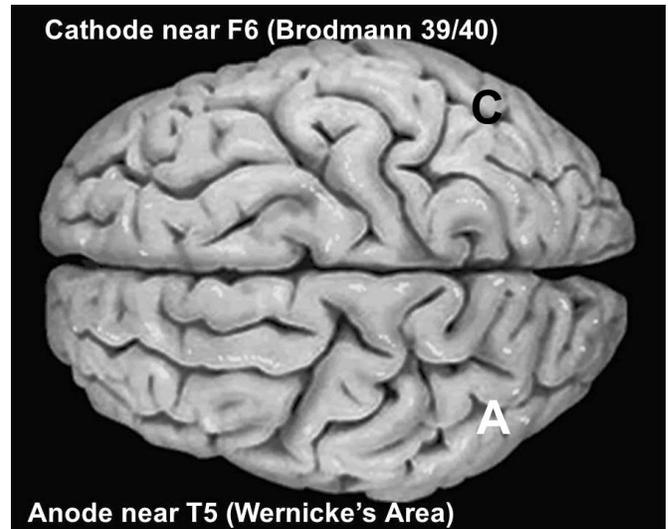


Figure 15. Treating Wernicke’s aphasia following stroke (Monti et al., 2013).

treatment montage for recovering speech and language following stroke (Monti et al., 2013).

Discussion

This article was meant to highlight some simple-to-use, low-cost brain STs, specifically AVE, CES, and tDCS. As a cautionary note, any neuromodulatory technique should be used with awareness of vulnerabilities, such as avoiding use during pregnancy, with individuals who are photosensitive (e.g., photosensitive epilepsy), or who have a pacemaker or other implanted life-preserving bioelectric appliances (Hallett et al., 2001; Southworth, 1999). Maslen, Douglas, Kadosh, Levy, and Savulescu (2014) would go farther in noting that cognitive enhancement devices should be regulated as medical devices, where any risks of use should be weighed against any potential gain from their use. For example, Maslen et al. (2014) suggested that risk assessment follow established guidelines based on the vulnerability of the user, where a normal healthy adult using STs may be at a lower risk compared to a very young child.

There are several decades of clinical studies providing evidence for the effectiveness of STs. It is gratifying that STs provide nonpharmaceutical and relatively low-cost methods for achieving beneficial outcomes, from addressing a variety of clinical symptoms to enhancing mental performance. STs of the types described in this article are well proven and should be part of the tool chest used by biofeedback practitioners working with generalized cognitive challenges including memory, affective disorders, and pain, including prophylactic, acute, and chronic applications.

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