Stress prevention by modulation of autonomic nervous system (heart rate variability): A preliminary study using transcranial direct current stimulation

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ABSTRACT

Introduction: Transcranial Direct Current Stimulation (tDCS) is a non-invasive, technique for brain stimulation. Anodal stimulation causes neuronal depolarisation and long-term potentiation, while cathodal stimulation causes hyperpolarisation and long-term depression. Stressors are associated with an increase in sympathetic cardiac control, a decrease in parasympathetic control, or both. Associated with these reactions is a frequently reported increase in Low Frequency (LF) Heart Rate Variability (HRV), a decrease in High Frequency (HF) power, and/or an increase in the LF/HF ratio. Objectives and Aims: The present work aims to explore the tDCS potential in the modulation of the Autonomic Nervous System (ANS), through indirect stimulation of Anterior Cingulate Cortex (ACC). Methods: Two subjects, a 39 year old female and a 49 year old male, gave informed consent. Saline soaked synthetic sponges involving two, thick, metallic (stainless steel) rectangles, with an area of 25 cm² each have been used as electrodes, connected to Iomed Phoresor II Auto device. It has been delivered a 2 mA current, for 20 minutes, over the left Dorsolateral Prefrontal Cortex (DLPFC) (Anode). Spectrum analysis (cStress software) of HRV has been performed before and after tDCS administration. Results: The female/male subject results of LF power, HF power and LF/HF ratio, before tDCS administration, were, respectively: 50.1 nu/60 nu, 46.1 nu/21.7 nu and 1.087/2.771; and, after tDCS administration, respectively: 33.5 nu/52.7 nu, 47.6 nu/22.8 nu and 0.704/2.312. Conclusions: tDCS over the left DLPFC (left ACC) increased parasympathetic activity and decreased sympathetic activity, suggesting the importance of tDCS in the management of stress-related disorders.

Keywords: Transcranial Direct Current Stimulation; Left Dorsolateral Prefrontal Cortex; Left Anterior Cingulate Cortex; Autonomic Nervous System; Heart Rate Variability; Stress

1. INTRODUCTION

1.1. Definition and Applications of Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) is a simple, non-invasive, technique for brain stimulation that induces prolonged functional changes in the cerebral cortex [1]; essentially it consists in delivering for a few minutes a weak direct current (below the perceptual threshold) over the scalp: the resulting constant electric field penetrates the skull and influences neuronal function. The electrical field of tDCS penetrating into the scalp induces changes in brain excitability. Stimulation of different cortical areas had resulted in modifications of perceptual, cognitive, and behavioral functions, and it can induce beneficial effects in brain disorders [2-27] (Figure 1). The tDCS is a form of neurostimulation that may be used to safely treat a variety of clinical conditions including depression, obsessive-compulsive disorder, Tourette’s disease, Alzheimer’s disease, migraine, and central and neuropathic chronic pain. It can also relieve the symptoms of narcotic withdrawal and reduce cravings for drugs, including nicotine and alcohol. It can be used to increase frontal lobe functioning and reduce impulsivity and distractibility in persons with attention deficit disorder; tDCS also boosts verbal and motor skills and improve learning and memory, in healthy people. Initial studies in humans aimed at treating or modifying psychiatric diseases, particularly depression. Anodal stimulation diminish depressive symptoms [28], while cathodal stimulation reduce manic symptoms [29]. The basic treatment consists of a series of five 20-minute...
sessions over five consecutive days. While the patient is seated, two 5 cm × 5 cm non-metallic conductive rubber electrodes are placed on selected locations of the scalp and covered by saline soaked sponges and held in place by elastic headbands. After the electrodes are properly placed, a tDCS device powered by a 9-volt battery is used to send a steady electrical current of 1 - 2 milliAmère (mA). Fregni et al. (2006) [27] reported on a randomized, sham-controlled, clinical trial of tDCS in the treatment of 10 patients diagnosed with major depression. The level of depression was evaluated before and after treatment by means of the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). Patients were randomly assigned to one of two groups, an active treatment group that received 1 mA anodal (electrode positively charged) tDCS over the Left Dorsolateral Prefrontal Cortex (DLPFC) and cathodal (electrode negatively charged) stimulation over the contralateral supraorbital area (just above right eyebrow) versus a sham treatment group that received the identical treatment but with the tDCS device turned off. Both groups received 20 minutes of actual or sham stimulation once a
day for five consecutive days. The active treatment group showed a significantly greater reduction in depression scores on the post-treatment HDRS and BDI as compared to the sham treatment group (70% versus 30%, respectively).

1.2. Mechanism of Action of Transcranial Direct Current Stimulation

Systematic animal studies in anesthetized rats demonstrated that weak direct currents, delivered by intracerebral or epidural electrodes induce cortical activity and excitability diminutions or enhancements, which can be stable long after the end of stimulation [30]. Stimulation with the negative pole (cathode) placed over a selected cortical region will decrease neuronal activity under the electrode whereas stimulation with the positive pole (anode) will increase neuronal activity under the electrode. Changes in spontaneous neuronal firing rates, coupled with synaptic neuroplasticity, contribute to intra- and post-stimulation effects respectively. The changes are long-lasting —5 to 10 minutes of continuous stimulation produced effects up to 5 hours afterwards. Anodal stimulation shifts neuronal resting membrane potential towards depolarisation, while cathodal stimulation shifts resting membrane potential towards hyperpolarisation. tDCS induces changes by altering the strength of synaptic transmission. Anodal toes could induce Long-Term Potentiation (LTP), through increased pre-synaptic activity coupled with postsynaptic depolarisation; conversely, cathodal toes could induce Long-Term Depression (LTD), through reduced presynaptic discharge and postsynaptic hyperpolarisation. The evidence for a neuroplastic synaptic contribution to the effects of tDCS is thus compelling. Respecting the physical parameters and practical application of tDCS, the efficacy of tDCS to induce acute modifications of membrane polarity depends on current density, which determines the induced electrical field strength [31], and is the quotient of current strength and electrode size. Larger current densities result in stronger effects of tDCS [32,33]. Another important parameter of tDCS is stimulation duration. With constant current density, increasing stimulation duration determine the occurrence and duration of after-effects in humans and animals [30,32,34,35]; direct currents are generally delivered via a pair of sponge electrodes moistened with tap water or NaCl solution (size between 25 and 35 cm² in different studies) [12,32,33,36,37]. Increasing focality of tDCS may be achieved by: 1) reducing electrode size, but keeping current density constant, for the electrode that is intended to affect the underlying cortex; 2) increasing the size, and thus reducing current density, of the electrode, which should not affect the underlying cortex; or 3) using an extra-encephalic reference. Regarding the time course of tDCS-induced modulations of cortical excitability, because increasing current density will increase cutaneous pain sensation and might affect different populations of neurons (because the larger the current density, the greater the depth penetration of the effective electrical field), it is suggested to increase stimulation duration and not current density, if a prolongation of the effects of tDCS for an extended time course is wanted [32,34,35]. When applied for several minutes, tDCS produces lasting effects in the human motor cortex. These are stable for up to about an hour if tDCS is applied for 9 - 13 minutes [32,34,35,38].

1.3. Safety Procedures of Transcranial Direct Current Stimulation

In relation with safety procedures, generation of electrochemically produced toxins and electrode dissolution products at the electrode-tissue interface are only risks of tDCS for the skin contact, because there is no brain-electrode interface. Subjects should be specifically interviewed for the existence of skin diseases (also in the past) and the condition of the skin under the electrodes should be inspected before and after tDCS. Conventional electrical brain stimulation can cause excitotoxic damage to overdriven neurons [39]. This is not applicable to tDCS. The stimulation device should guarantee a constant current strength, because current strength determines the intensity of the electrical field in tissue and a constant voltage device could result in unwanted increases in current strength, if resistance decreases. Stimulation durations, which are likely to result in excitability changes lasting more than one hour, should be applied with caution, because changes lasting that long could be consolidated and stabilized, leading to unintended or adverse effects. The same applies for repeated application of tDCS to the same brain region without an appropriate interval between sessions. Subjects should be free of any illness that may increase the risk of stimulation, for example, neurologic diseases such as epilepsy or acute eczema under the electrodes. Furthermore, they should have no metallic implants near the electrodes. Seizures do not appear to be a risk for healthy subjects; however, this may not be true for patients with epilepsy [40].

2. MODULATION OF AUTONOMIC NERVOUS SYSTEM (HEART RATE VARIABILITY) BY TRANSCRANIAL DIRECT CURRENT STIMULATION: A PILOT STUDY PRELIMINARY RESULTS WITH IMPORTANCE TO RESILIENCE TO STRESS SCIENCE

2.1. Heart Rate Variability

The heart is a pump, though a complex one in structure and regulation, with two sides—a left side and right side
The regulation of Cardiac Output (CO) under conditions of stress. Stress results in activation of the two branches of the Autonomic Nervous System (ANS), and of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Activation of the Sympathetic branch (SNS) results in PNS withdrawal, demonstrated by a reduction in High-Frequency (HF) Heart Rate Variability (HRV), and consequent increase in Heart Rate (HR). Activation of the Sympathetic branch (SNS) results in secretion of Noradrenaline (NE) and Epinephrine (EPI), and consequent increase in both cardiac contractility and HR. Activation of the HPA axis is demonstrated by secretion of cortisol by the adrenal cortex, which both potentiates the effects of NE and EPI, and independently contributes to the same effects as these catecholamines. Respecting the regulation of smooth muscle tone under conditions of stress, activation of SNS results in Parasympathetic (PNS) withdrawal (reduction of HF-HRV). The consequent effects on the healthy endothelium are vasodilatation, but, in the presence of atherosclerotic disease, vasocostriction. PNS withdrawal leads to an increased release of pro-inflammatory cytokines—Interleukin-6 (IL-6)—and vasactive proteins—Intercellular Adhesion Molecule (sICAM)—from macrophages, due to the resulting disinhibition. Activation of the SNS results in secretion of NE and EPI, with consequent effects on vascular smooth muscle. Release of NE causes vasoconstriction, through its action on α-receptors. EPI released into the circulation, from the adrenal medulla, provokes an opposite vasodilating effect, through its action on β1-receptors. Activation of HPA axis, and subsequent secretion of cortisol, both potentiates the effects of NE and EPI, and, independently, contributes to the down-regulation of the inflammatory response, through its action on IL-6, though in the presence of atherosclerotic disease, this negative feedback loop is impaired. Stress contributes to oxidative (O2) stress, which contributes to endothelial dysfunction and consequent vasoconstriction, with Endothelin-1 (ET-1) playing an essential role (Adapted, with permission, from The Cardiovascular System, by Mathew, MB, Pickering, TG, in The Handbook of Stress Science: Psychology, Medicine and Health, edited by Contrada, RJ, Andrew, B, Springer Publishing Company, Inc. 2011).
end systolic volume. These volumes are determined by wide ranging factors including: venous return or preload, which contributes to the degree of stretch in the wall of the ventricle; because of the nature of myocardial tissue, an increase in venous return results in an increase in end diastolic volume and associated muscle stretch and, hence, an increase in stroke volume; and after-load, reflected in TPR. All of these factors will typically vary in an ongoing manner as determined by moment to moment changes in tissue metabolic requirements and ANS tone. The SNS stimulation can profoundly increase the Heart Rate (HR) (contractions per minute), the speed of individual ventricular contractions, and the force of these contractions (for example, shorter systolic and diastolic intervals, more forceful ejection, and faster acceleration of ventricular outflow velocities). Conversely, PNS stimulation can have immediate and profound effects, by slowing the heart rate. The vascular system—specifically its arterial branch—serves as a branching system that directs blood to each bodily organ according to its needs, and also serves as a “pressure reservoir” that absorbs the pulsations in blood flow produced by the alternating contraction and relaxation of the heart’s ventricles. A reduction of arterial elasticity is one of the first alterations that can be observed along the path toward essential hypertension. Diastolic and systolic pressure can vary substantially as a function of metabolic needs and physical and emotional stress, though diastolic pressure is prevented by bodily reflexes from dropping below 40 and 60 mmHg so as to ensure a level of perfusion to the brain necessary to maintain consciousness. Cross-sectionally, arteries are described by a lumen, the open interior through which blood passes. A single layer of endothelial cells surrounds the lumen and this cellular layer is in turn surrounded by a thicker layer of smooth muscle cells—these two layers provide avenues by which the ANS and other local processes dynamically regulate vascular tone. Smaller arteries and arterioles that are further along the arterial tree are notable for their greater muscularity, which allows them to serve as sphincters, that vasoconstrict or vasodilate, and thereby control the flow of blood to the capillary beds they serve, and it is through this involuntarily regulated function, blood flow to each bodily organ is precisely controlled according to factors that include relative local and systemic metabolic needs associated with levels and types of activity. Although perfusion to the organs can vary according to relative needs (increased blood flow to large muscles and heart can be associated with relative decrease in blood flow to digestive organs as observed during the “fight-flight” response), perfusion to the brain must be kept constant. Having passed through the capillary bed, the flow of blood in the venous return system is at a low pressure and moves proportionately slower (in contrast to arteries, therefore, veins have a larger lumen and thinner walls, so that resistance to flow is reduced). Internal one-way valves ensure that blood flows back to the heart, whereas contractions of muscles around the veins, such as those in the legs and abdomen, support the flow of blood against the force of gravity as it returns from the lower body and extremities back to the heart. Regulation of the circulation (Figure 2) is achieved by a combination of brain activity with local regulatory mechanisms: monitoring changes of oxygenation is accomplished by chemoreceptors, and arterial pressure, is accomplished by baroreceptors. Increased metabolic activity in muscles depletes oxygen and increases levels of carbon dioxide and associated chemical reactants, and chemoreceptors detect these changes and, in addition to signalling the brain that there is a need for increased respiration, provoke relative dilation in local microvascular smooth muscle to increase blood flow and thereby provide the oxygen needed to support the continued work of the muscle. Reactive hyperemia, an auto-regulatory process by which the vascular endothelium responds with significant nitric oxide provoked dilation after release of temporary occlusion of blood flow, provides an example of the underlying mechanism. Baroreceptors, with the most sensitive being found in carotid sinuses and aortic arch, comprise part of a system of Central Nervous System feedback loops that control ANS activity in the service of Blood Pressure (BP) regulation. SNS activation leads to an elevation of TPR and CO (via increased cardiac contractility, heart rate and arterial vasoconstriction, which together tends to increase BP). Conversely, PNS activation leads to a decreased CO (via decreased HR, resulting in a tendency to lower BP). SNS and/or PNS inhibition produces opposite results. When BP rises, the carotid and aortic sinuses are distended, resulting in stretch and therefore activation and firing of the baroreceptors. Alternatively, when BP drops, firing of baroreceptors decreases. Baroreceptor activation provokes inhibition of SNS activity and excitation of PNS activity. By coupling relative SNS inhibition and PNS activation, the baroreflex maximizes BP regulation. SNS inhibition leads to a drop in TPR, whereas PNS activation leads to depressed heart rate and myocardial contractility, which will dramatically decrease BP. Conversely, a decrease in BP is detected by baroreceptors, and, through these circuits, increases SNS activation, inhibits PNS activity and, through an increase in CO and TPR, elevates BP. The analysis of Heart Rate Variability (HRV) allows the observation of the fluctuations of HR during worship time periods or long periods and is a non-invasive and selective observation of the ANS function. These methods include simple statistics, such as the standard deviation
of HR or RR interval. For analysis of cardio-vagal function, the methods developed for clinical trials typically involve the measurement of HRV over short intervals of time (<90 seconds) [41,42]. To study the ANS under various conditions such as physiological, psychological and pathological, non-invasive analysis of spectral power in RR intervals has been used very recently [43]. The power spectrum is determined by measuring the area under the band of two frequencies: Low Frequency (LF) power, calculated from 0.04 to 0.15 Hz, and High Frequency (HF), whose power ranges from 0.15 to 0.40 Hz. The clinical usefulness of HRV to identify changes in the ANS, diseases of the heart, has been enhanced by the use of different methods of study. Time domain variability is measured by the statistical and geometric method, and the selection of each match the objective of each particular case. The study in the frequency domain is related to the analysis of the spectral density, which studies how power (variance) distributes as a function of frequency, i.e., spectral analysis decomposes the total HRV in their causing components, presenting them according to the frequency with which changes the HR. For the calculations of spectral density, are commonly used nonparametric (Fast Fourier Transform) and parametric (autoregressive model) methods, and these allow the reading of the same results, tough each have their own advantages. They decompose a signal in its frequency components, and, regardless of the calculation of the spectral density (non-parametric or parametric), it is usually delimited three distinct frequency bands, called spectral components [42,44], which are: the frequency band < 0.003 Hz (Ultra Low frequency: ULF) and the frequency band from 0.003 to 0.04 Hz (Very Low Frequency: VLF) represent actions of humoral regulation, vasomotor and temperature and the activity of renin-angiotensin-aldo-sterone system. The frequency band of 0.04 to 0.15 Hz (Low Frequency: LF) reflects the SNS and PNS modulation tone, through the baro-reflex activity (regulation of BP). The frequency band from 0.15 to 0.45 (High Frequency: HF) is the modulation of the vagal activity. With advancing age, HRV suffers a decline, i.e., varies less. In the normal population without pathological signs, HRV shows broad limits due to the adjustment of the ANS and age. Changes in posture, emotions, time of day or night can induce changes in this same variability [45]. With regard to gender, there are reports that middle-aged men present predominantly lower HRV when compared with women of similar age [46]. A reduced HRV is presented as a powerful predictor of arrhythmic complications resulting from a myocardial infarction and of mortality [42]. The weight also influences HR and HRV. Another factor that influences HRV has to do with exercise—exercise itself is a behavior that provokes important changes in the functioning of the cardiovascular system and its mechanisms of autonomic adjustments [47].

2.2. Connectivity between Anterior Cingulate Cortex and Dorsolateral Prefrontal Cortex

The anatomical and functional connections between DLPFC and medial prefrontal cortex, including Anterior Cingulated Cortex (ACC) and orbitofrontal cortex, have been documented by anatomical and neuroimaging studies [48-52]. ACC is the frontal part of the cingulate cortex—resembling a “collar” form around the corpus callosum, the fibrous bundle that relays neural signals between the right and left cerebral hemispheres of the brain—and it consists of Broadmann areas 24, 32 and 11, appearing to play a role in a wide variety of autonomic functions, such as regulating BP and HR, as well as rational cognitive functions (reward anticipation, decision making, empathy, emotion). ACC can be divided anatomically based on cognitive (dorsal), and emotional (ventral) components—the dorsal part of the ACC is connected with the prefrontal cortex and parietal cortex as well as the motor system and the frontal eye fields, making it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain; the ventral part of the ACC is connected with amygdala, nucleus accumbens, hypothalamus, and interior insula, and is involved in assessing the salience of emotion and motivational information. The adjacent subcallosal cingulate gyrus has been conjectured to play an important role in major depression, and has been the target of deep brain stimulation to treat that disease [53]. Using indices of HRV, and HF and LF power in the cardiac rhythm, Critchley et al. (2003) observed activity in the dorsal ACC related to sympathetic modulation of HR that was dissociable from cognitive and motor-related activity, and their findings predict that during effortful cognitive and motor behaviour the dorsal ACC supports the generation of associated autonomic states of cardiovascular arousal (neuroimaging and clinical findings suggest that ACC function mediates context-driven modulation of bodily arousal states) [54].

2.3. Summary of Transcranial Direct Current Stimulation and Heart Rate Variability

Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique for brain stimulation. Anodal stimulation causes neuronal depolarisation and long-term potentiation, while cathodal stimulation causes hyperpolarisation and long-term depression. Stressors are associated with an increase in sympathetic cardiac control, a decrease in parasympathetic control, or both. Associated with these reactions is a frequently reported increase in LF HRV, a decrease in HF power, and/or an increase in
Figure 3. HRV parameters result (Cstress Analysis)—Total Peak, VLF Peak, LF Peak, HF Peak, Total Power, VLF Power, LF Power, HF Power and LF/HF ratio—before (3.1) and after (3.2) tDCS (using stimulator Phoresor II Auto model from Iomed Inc., USA) in the male subject, and before (3.3) and after (3.4) tDCS in the female subject.
the LF/HF ratio.

2.4. Objectives and Aims
The present work aims to explore the tDCS potential in the modulation of ANS, through indirect stimulation of ACC.

2.5. Methods
Two subjects, a 39 year old female and a 49 year old male, gave informed consent. Saline soaked synthetic sponges involving two, thick, metallic (stainless steel) rectangles, with an area of 25 cm² each have been used as electrodes, connected to Iomed Phoresor II Auto device. It has been delivered a 2 mA current, for 20 minutes, over the left DLPFC (Anode). Spectrum analysis (cStress software) of HRV has been performed before and after tDCS administration.

2.6. Results
The female/male subject results of LF power, HF power and LF/HF ratio, before tDCS administration, were, respectively: 50.1 nu/60 nu, 46.1 nu/21.7 nu and 1.087/2.771; and, after tDCS administration, respectively: 33.5 nu/52.7 nu, 47.6 nu/22.8 nu and 0.704/2.312 (Figure 3).

2.7. Limitations
The present study is limited by the quantity of research subjects; it is deprived of the blinding- and sham-control nature in its design.

2.8. Conclusions

2.9. ACKNOWLEDGEMENTS
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