The efficacy of use of transcranial direct current stimulation in the treatment of neurological disease & defect

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THE EFFICACY OF USE OF TRANSCRANIAL DIRECT CURRENT STIMULATION IN THE TREATMENT OF NEUROLOGICAL DISEASE & DEFECT

by

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B.A., Vanderbilt University, 2010

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Master of Arts

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Non-invasive brain stimulation techniques have recently become popular in the treatment of neurological diseases and disorders. Transcranial direct current stimulation [tDCS] is a method of brain stimulation whereby direct electrical current is passed through the intact scalp into the nervous tissue, producing lasting changes in neural activity of the stimulated areas. The polarity, or direction, of current flow in relation to the orientation of neural networks determines whether neuronal activity is enhanced or inhibited. The lasting increases or decreases in neuronal activity produced by tDCS have been used to shape cognitive function in various neurological diseases and disorders, including stroke, Parkinson’s disease, Alzheimer’s disease and depression.

Currently, the mechanism of action for the effects caused by tDCS is not well understood. The goal of this thesis is to evaluate the efficacy of tDCS as a therapy for these brain disorders. The vast majority of these studies found strong and largely consistent evidence
for the improvement of symptoms following tDCS for periods lasting up to several weeks when applied appropriately. While further refinement is needed to expand the effectiveness of tDCS treatment, the future looks promising.
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  Use of tDCS in Stroke

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  Mechanism of Pathology
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Alzheimer’s Disease
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<td>ACTH</td>
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<td>Alzheimer’s Disease</td>
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<td>ADAS-cog</td>
<td>Alzheimer Disease Assessment Scale-cognitive</td>
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<td>ADP</td>
<td>Adenosine Diphosphate</td>
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<td>ALP</td>
<td>Autophagy Lysosome Pathway</td>
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<td>AMPA</td>
<td>alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid</td>
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<td>APOE-ɛ4</td>
<td>Apolipoprotein E type 4</td>
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<td>APP</td>
<td>Amyloid Precursor Protein</td>
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<td>ASIC</td>
<td>Acid-Sensing Ion Channel</td>
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<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
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<td>AVM</td>
<td>Arteriovenous Malformation</td>
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<td>BACE</td>
<td>beta-APP-Cleaving-Enzyme</td>
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<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>CA1</td>
<td>Region 1 of hippocampus proper</td>
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<td>Ca++</td>
<td>Calcium Ion</td>
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<td>CDR</td>
<td>Clinical Dementia Rating</td>
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<td>CIMT</td>
<td>Constraint Induced Movement Therapy</td>
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<td>CM</td>
<td>Centromedial nucleus of the Thalamus</td>
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<td>COMT</td>
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<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
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<tr>
<td>cTBS</td>
<td>Continuous Theta Burst Stimulation</td>
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<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>DBS</td>
<td>Deep Brain Stimulation / Stimulator</td>
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<td>Dorsolateral Prefrontal Cortex</td>
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<td>DMO</td>
<td>Dextromorphan</td>
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<td>DMPFC</td>
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<td>Deoxyribonucleic Acid</td>
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<td>DRN</td>
<td>Dorsal Raphe Nucleus</td>
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<td>ECT</td>
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<td>Electromyography</td>
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<td>FLU</td>
<td>Flunarizine</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>gamma-Aminobutyric Acid</td>
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<td>GDNF</td>
<td>Glial Derived Neurotrophic Factor</td>
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<td>Internal Segment of the Globus Pallidus</td>
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<td>ICF</td>
<td>Intracortical Facilitation</td>
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<td>IHI</td>
<td>Interhemispheric Inhibition</td>
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<td>ISI</td>
<td>Interstimulus Interval</td>
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<td>iTBS</td>
<td>Intermittent Theta Burst Stimulation</td>
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<td>Acronym</td>
<td>Abbreviation</td>
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<tr>
<td>JTT</td>
<td>Jebsen-Taylor Hand Function Test</td>
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<tr>
<td>K+</td>
<td>Potassium</td>
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<tr>
<td>LB</td>
<td>Lewy Body</td>
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<tr>
<td>LN</td>
<td>Lewy Neurite</td>
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<tr>
<td>LTD</td>
<td>Long-Term Depression</td>
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<td>LTP</td>
<td>Long-Term Potentiation</td>
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<td>MADRS</td>
<td>Montgomery–Asberg Depression Rating Scale</td>
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<td>MAO</td>
<td>Monoamine Oxidase</td>
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<td>Major Depressive Disorder</td>
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<td>MEP</td>
<td>Motor Evoked Potential</td>
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<tr>
<td>mEPSC</td>
<td>Miniature Excitatory Post-Synaptic Current</td>
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<td>MMSE</td>
<td>Mini Mental State Exam</td>
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<td>MPTP</td>
<td>1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine</td>
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<td>Sodium</td>
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<td>NFT</td>
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<td>NIH</td>
<td>Nation Institutes of Health</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
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<tr>
<td>NO</td>
<td>Nitric Oxide</td>
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<tr>
<td>NOS</td>
<td>Nitric Oxide Synthase</td>
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<td>PARP1</td>
<td>Poly [ADP-ribose] polymerase 1</td>
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<td>PAS</td>
<td>Paired Associative Stimulation</td>
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<td>PCC</td>
<td>Posterior Cingulate Cortex</td>
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<td>PD</td>
<td>Parkinson’s Disease</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PID</td>
<td>Peri-Infarct Depolarization</td>
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<td>PPN</td>
<td>Pedunculopontine Nucleus</td>
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<td>PPT</td>
<td>Purdue Pegboard Test</td>
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<td>PT</td>
<td>Pyramidal Tract</td>
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<td>rTMS</td>
<td>Repetitive Transcranial Magnetic Stimulation</td>
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<td>SACC</td>
<td>Supragenual Anterior Cingulate Cortex</td>
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<td>SICI</td>
<td>Short Interval Intracortical Stimulation</td>
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<td>SMER</td>
<td>Small Molecule Enhancers</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>SNC</td>
<td>Substantia Nigra Pars Compacta</td>
</tr>
<tr>
<td>SNR</td>
<td>Substantia Nigra Pars Reticulata</td>
</tr>
<tr>
<td>SP</td>
<td>Senile Plaque</td>
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<tr>
<td>sRT</td>
<td>Simple Reaction Time</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin-Reuptake Inhibitor</td>
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<tr>
<td>STN</td>
<td>Subthalamic Nucleus</td>
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<tr>
<td>TBS</td>
<td>Theta Burst Stimulation</td>
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<td>tDCS</td>
<td>Transcranial Direct Current Stimulation</td>
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<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
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<tr>
<td>TP</td>
<td>Temporoparietal</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue Plasminogen Activator</td>
</tr>
<tr>
<td>TrkB</td>
<td>Tyrosine related kinase BDNF</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson Disease Rating Scale</td>
</tr>
<tr>
<td>UPS</td>
<td>Ubiquitin-Proteasome System</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
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<td>Acronym</td>
<td>Description</td>
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<td>VAT</td>
<td>Visual Attention Task</td>
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<tr>
<td>VLa</td>
<td>Anterior Portion of the Ventrolateral Nucleus</td>
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<td>VRM</td>
<td>Visual Recognition Memory</td>
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<td>VRT</td>
<td>Visual Recognition Task</td>
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<td>VS</td>
<td>Ventral Striatum</td>
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<td>VTA</td>
<td>Ventral Tegmental Area</td>
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<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

The major functional unit of the nervous system is the neuron. While there are many different types, all neurons operate via basic electrical principals. Electrical signals are sent to, from, and along neurons encoded electrochemically via changes in ionic density (or concentration). Thus the function of neurons, and their contiguous communication, can be modulated by any technique that alters their electrochemical properties.

The use of electricity to treat neurological disorders can be traced back to the first century A.D., when a Roman physician, Scribonius Largus, used Mediterranean electric rays to treat headaches (Wagner et al., 2009). While the effect of direct current stimulation on neural tissue was discovered in the 1960s, it was not until the turn of the century that it began to be used in studies of cognitive neuroscience and neurological disorders.

Transcranial direct current stimulation [tDCS] is a non-invasive method of electrical brain stimulation that produces lasting changes in the activity of stimulated neurons. TDCS can increase or decrease neuronal activity and produce resultant changes in behavior in stimulated areas. The electrical fields induced by tDCS are most likely the basis of the changes observed in neural activity. Because of its ability to shape cognitive function in targeted brain areas, tDCS has great potential for treating neurological diseases and disorders.
The goal of this thesis is to determine the current state of knowledge of the neurobiology of tDCS and to critically evaluate its application as therapy for various neurological diseases and disorders. TDCS is presently being used to treat a host of disorders, such as stroke and brain trauma, depression, addiction, pain and headaches, and various neurological diseases such as Alzheimer’s disease, Parkinson’s disease, and Schizophrenia. For future studies it is important to optimize the efficacy of tDCS as a treatment therapy. This can be accomplished by careful analysis of pathogenesis of each disease in conjunction with the neural effects of tDCS.

HISTORY

In 1964 Bindman and colleagues investigated the effect of weak polarizing direct current on neuronal activity. Using microelectrodes to record extracellular potentials in grey matter or from the pial surface of anaesthetized rats, they found that a small amount of surface-positive (anodal) current [tip-electrode: 0.1 - 0.3μA or 60 -250μA/mm2; surface electrode: 20 - 25μA or 40 - 50μA/mm2] applied for a few minutes (up to 20 minutes) caused an increase in both the spontaneous firing rate and the amplitude of evoked potentials in nearby recorded neurons. Inhibition of neurons, reduced amplitude of evoked potentials, and lowered spontaneous firing rate were observed during surface-negative cathodal current. A few minutes of either anodal or cathodal stimulation produced neural effects that lasted anywhere from minutes to several hours (at least 5 hours in some cases) if current was applied for 5 minutes or longer. Short bursts of high current density (200μA or 400μA/mm2) abolished all electrical activity for a short
duration. Similarly, abolition of electrical activity was also observed when the distance between the neuron and tip electrode was within a certain distance (Bindman et al., 1964).

A subsequent study by Purpura and McMurty used contemporaneous intra- and extracellular recordings of neurons to study the effects of direct current on neurons in the primary motor cortex. They first identified pyramidal tract [PT] cells using antidromic stimulation of the medullary pyramidal tract in *encephale isole* cats. The intra- and extracellular activity of PT and other non-PT surrounding cells was monitored during stimulation of the ventral lateral nucleus of the thalamus, which provides input to the primary motor cortex. They found that anodal direct current stimulation depolarized the resting membrane potential while cathodal stimulation hyperpolarized the resting membrane potential. When recording from cells at depths near or below 1 mm, an increase in spontaneous activity and amplitude of evoked action potentials occurred during anodal surface polarizing stimulation and a decrease in spontaneous activity and evoked potential amplitude occurred during cathodal stimulation. At more superficial depths, above 0.9 mm, they noticed both anodal and cathodal stimulation had reversed effects during surface polarizing stimulation (Purpura & McMurty, 1965).

These two studies showed that surface-positive (anodal) direct current stimulation increased spontaneous firing rates and the amplitude of evoked potentials while surface-negative (cathodal) stimulation decreased the firing rate and amplitude of evoked potentials. These effects were due to an increase or decrease of the resting membrane
potential caused by the anodal or cathodal stimulation, respectively. These effects appeared to also be related to the orientation and architectonic properties of exposed nervous tissue in relation to the flow of electrical current and the resulting polarity of the induced electrical field. More simply, when an electrical field is present it may influence the electrical properties of neurons differently based on location and alignment in relation to the induced electrical field.

It is important to note that these seminal papers used direct current stimulation of the exposed cortex. For many years, these findings were neglected and the results relegated to the domain of basic science. However, in 2000, Nitsche and Paulus published a paper that showed that the effects of a weak direct current on neural activity and behavior could be observed even when the direct current electrodes were placed on the scalp. This technique was called transcranial direct current stimulation, and has become incredibly popular in the intervening years principally because of its ability to non-invasively modulate brain activity in humans.

Nitsche and Paulus used $35 \text{cm}^2$ saline-soaked sponge electrodes and applied between 0.2 and 1.0 mA of current to the scalp for durations varying between 1 and 5 minutes using an array of electrode positions. They used Transcranial Magnetic Stimulation [TMS] to stimulate specific areas of primary motor cortex and then monitored the changes in amplitude and frequency of resulting Motor Evoked Potentials (MEPs) recorded in right abductor digiti minimi muscle. They found that placement of the primary (active) electrode above primary motor cortex and the secondary (indifferent)
electrode at the contralateral forehead area produced the greatest physiological changes. They discovered that at a threshold of 0.6mA of current intensity and 3 minutes of stimulation duration, tDCS produced lasting changes in the amplitude of the MEP evoked by stimulation of the primary motor cortex. These effects were characterized by increased MEP amplitude after anodal stimulation and decreased MEP amplitude after cathodal stimulation to the active electrode. These findings indicated that the excitability of the motor cortex could be bidirectionally modified by weak transcranial electrical current. Increasing the current intensity or the duration of electrical stimulation resulted in an increase in the duration of these observed aftereffects (Nitsche & Paulus, 2000).

**BASIS OF tDCS**

Theoretically, tDCS induces electrical fields in the brain based on the polarity of current flow and depending on the location of the electrodes. While there are many potential ways to apply electrical current to the brain, the methods from the 2000 study by Nitsche and Paulus are the standard for applying tDCS (Nitsche et al., 2003; Nitsche et al., 2007; Fricke et al., 2010; Reis et al., 2009; and others). Almost all investigations involving tDCS use 35cm² saline-soaked sponge electrodes and apply a current of approximately 0.5 – 1.5mA for periods between 5 and 35 minutes. Many investigations also use TMS to induce MEPs in peripheral muscles and then measure MEP amplitude using electromyography [EMG]. Changes in MEP amplitude correlate to changes in neuronal excitability in the primary motor cortex and can be used to measure the effect of stimulating techniques like tDCS. However, because this approach is limited to
monitoring motor-related events, many studies use other techniques to identify areas and measure changes, such as magnetic resonance imaging [MRI]-based methods, physical and mental assessments, and electroencephalography [EEG] (Marchand et al., 2010; Grimm et al., 2008; Lindenberg et al., 2012; DaSilva et al., 2012).

**MECHANISM OF ACTION**

The mechanism underlying tDCS is thought to be the alteration of the resting membrane potential of large populations of neurons, as suggested by the studies of Bindman (Bindman et al., 1964) and Purpura and McMurtry (1965). Cathodal stimulation biases resting membrane potentials towards hyperpolarized potentials, and makes the cells less excitable, whereas anodal stimulation produces a slight depolarization and makes the cell more likely to produce action potentials in response to a stimulus of a certain magnitude.

These explanations apply to the neural effects of tDCS during its application. A central and unresolved issue in the discussion of tDCS and its mechanism of action is the mechanisms underlying the lasting modification of neural activity. The means by which neural activity is changed by tDCS does not appear to accord with traditional studies of experimentally-induced long-lasting neuroplasticity.

Studies of neuroplasticity have their roots in a theoretical evaluation introduced in 1949 by Donald Hebb. He postulated that the efficacy of inducing post-synaptic responses arose from the timing and persistence of pre-synaptic stimulation (Hebb, 1949; Huang et al., 1992; Stefan et al.; 2000). This theoretical study was confirmed in studies
involving the hippocampus (Bliss & Lomo, 1973). This study found that repeated high frequency stimulation leads to the prolonged strengthening of signal transmission in a neuronal circuit, a phenomenon referred to as long-term potentiation (LTP). LTP is usually associated with synchronous neural activity that causes strengthening of synaptic connections via structural enhancements such as recruitment and augmentation of specific neurotransmitters, receptors, and other core components in the synaptic cleft. Another mechanism of plasticity, termed long-term depression [LTD], is a prolonged weakening of signal transmission. These two mechanisms of plasticity are often investigated for their connection to learning and memory in the hippocampus and elsewhere in the brain. Similar mechanisms, coined “LTP-like” and “LTD-like,” are being investigated for their connection to plasticity in higher-order areas of the brain (Monte-Silva et al., 2012; Fricke et al., 2010).

The synchronicity of synaptic activity is very important in the process of neuronal plasticity; small fluctuations in timing can result in very different outcomes. This was demonstrated in a 1997 study by Markram and his colleagues when they discovered that a difference of 10 milliseconds when evoking post-synaptic potentials from large pyramidal cells alters the amplitude of excitatory post synaptic potentials [EPSPs], proving that up- or down-regulation of EPSP amplitude is sensitive to very small timing differences. This suggests that the activity and timing of a single pyramidal cell affects every excitatory synapse within 100 milliseconds (Elbert & Rockstroh, 2004) and may have profound implications for LTP and LTD.
Additionally, neuronal plasticity may be homeostatic in nature, meaning individual neurons can regulate their own excitability relative to neural activity. The idea of homeostatic plasticity was first described in 1992 when it was discovered that prior neuronal activity influences the threshold for LTP induction (Huang et al., 1992). In 1998 Turrigiano and colleagues observed that total synaptic strength is regulated as a function of activity. Specifically, they found that the overall excitability of neurons did not change even when synaptic activity was blockaded or enhanced. This was accomplished by increases or decreases in the amplitude of miniature excitatory post synaptic currents [mEPSCs]. These mEPSCs summate and define the excitability of the neuron. Thus by altering mEPSC amplitudes over a period of 48 hours, neurons are able to maintain a constant level of excitation despite modulation of synaptic activity. This “synaptic scaling,” or homeostatic plasticity, allows neurons to effectively moderate their own excitability over time in spite of changes to neural input, which may help to keep firing rates below saturation during development and facilitate competition between synapses (Turrigiano et al., 1998). Homeostatic plasticity allows for each neuronal input to be inversely correlated with the amount of background activity. Without this balancing of neuroplasticity neuronal networks would destabilize (Nitsche et al., 2007).

Unlike homeostatic plasticity, associative or “Hebbian” plasticity is not regulated by the neuron itself in response to general neural activity, but occurs as a result of concomitant or synchronous activity or input to the post-synaptic cell. As the name suggests, the correspondence of timing similarity of input with other inputs, or the depolarization of the post-synaptic cell itself, causes an “association” between the events.
This typically leads to the phenomenon known as associative LTP, where the synapses (inputs) are strengthened depending on the timing and frequency of the “association.”

Associative plasticity was first demonstrated in human motor cortex by Stefan and colleagues in their 2000 study. In this experiment they developed a procedure for paired associative stimulation [PAS], which is still used in cognitive studies today. The basic concept involved concurrent low-frequency (0.05 Hz) stimulation of primary motor cortex with a TMS pulse and stimulation of the associated peripheral nerve with electrical current from a surface electrode. They measured MEP amplitude before and after, and also measured the duration of electrical silence that followed the MEP. By slightly altering the interstimulus interval [ISI], or duration between TMS pulse and peripheral nerve stimulation, they determined that an ISI of 25 msec, which results in simultaneous arrival of the stimuli to motor cortex, leads to significantly increased MEP amplitude and greater duration of the silent period after the 30 minute PAS session. This effect, increased MEP amplitude, remained present for at least 60 minutes, but were absent after 24 hours. This experiment confirmed that simultaneous peripheral and intracortical stimulation of motor cortex leads to LTP, or LTP-like enhancement; however, the lack of persistence of effects beyond a few hours suggests that structural changes, such as synaptogenesis and sprouting of intracortical fibers, are not responsible for the plasticity (Stefan et al., 2000).

The major mechanisms of synaptic plasticity are all based on changing the frequency and timing of neuronal inputs to produce lasting changes in the efficacy and
strength of pathways. Since tDCS uses a direct current, it is unlikely that it modulates activity through such frequency-dependent means.

In a 2010 study, Fritsch and colleagues used direct current stimulation in a mouse cortical slice preparation, and generated evoked potentials in superficial cortical areas by pulsed stimulation (0.1 Hz) of deep cortical layers. They found that anodal stimulation produced a lasting increase in evoked potential amplitude, and determined that this neuroplastic response to direct current stimulation depended on brain-derived neurotrophic factor [BDNF] secretion and tyrosine-related kinase B [TrkB] receptor activation. Plasticity was not observed in the same experimental paradigm when BDNF and TrkB mutant mice were used. Cathodal tDCS did not show any effect on neural activity in this study, suggesting that the lasting effects of cathodal tDCS on neural activity may be mediated by different mechanisms (Fritsch et al., 2010).

**NEUROBIOLOGY OF tDCS**

**THE EFFECTS OF tDCS ON NEUROPLASTICITY:**

Transcranial direct current stimulation is used because it non-invasively enhances or inhibits cortical excitability. The application of tDCS has been dictated largely by the initial study of tDCS (Nitsche & Paulus, 2000), but a great deal of effort has been applied to determine how the effects of tDCS changes with the electrical and temporal parameters of the applied current.
In 2007, Nitsche and colleagues investigated how the widespread cortical modulation caused by tDCS influences associative, synapse-specific plasticity in the human motor cortex. They used previously defined protocols for both tDCS (Nitsche & Paulus, 2000) and PAS (Stefan et al., 2000) to test their hypothesis. They wanted to understand how homeostatic plasticity influenced associative plasticity. More specifically, they wanted to determine how anodal and cathodal tDCS affects PAS-induced neuroplasticity.

They first performed a set of control experiments to demonstrate how differences in duration of PAS or tDCS affected motor cortex excitability. They determined that 7 min of PAS (short-term) resulted in increased MEP amplitudes that lasted approximately 25-30 minutes. Next they determined that 15 minutes of PAS (long-term) resulted in a greater increase in MEP amplitude that lasted up to 60 minutes. In separate experiments, they confirmed that 7 minutes of anodal tDCS increased excitability for approximately 30 minutes, while 7 minutes of cathodal tDCS decreased excitability for approximately the same amount of time (Nitsche et al., 2007).

They proceeded to perform a series of experiments to determine how the effects of tDCS interacted with the associative plasticity induced by PAS. They found that the consecutive treatment of 7 minutes of anodal tDCS followed by 7 minutes of PAS resulted in increases in MEP amplitude that lasted for a longer duration (up to 90 minutes) than seen with tDCS or PAS alone. When anodal tDCS was administered simultaneously with short-term PAS a decrease in excitability was observed lasting up to
30 minutes. Consecutive treatment of 7 minutes of cathodal tDCS followed by short-term PAS resulted in mild decreases in MEP amplitudes compared to baseline activity, which was similar to effects caused by cathodal tDCS alone. However, simultaneous cathodal tDCS and short term PAS resulted in an increase in excitability that was greater than the effects caused by 7 minutes of PAS alone; more similar to the effects seen after 7 minutes of anodal tDCS. Finally, 15 minutes of anodal tDCS administered simultaneously with long-term PAS resulted in MEP amplitude reduction that lasted longer than 24 hours (Nitsche et al., 2007).

This experiment shows that when tDCS and PAS are administered consecutively they act in a more synergistic and additive manner; increases in excitability by anodal tDCS is further enhanced by PAS and decreases in excitability by cathodal tDCS are diminished by excitability-inducing PAS. However, when tDCS and PAS are administered simultaneously the excitability induced from PAS is affected by tDCS-induced changes in background activity. This demonstrates that associative plasticity is influenced by homeostatic mechanisms, or more simply, the intrinsic excitability of each neuron influences the plasticity of the group. Assuming that tDCS alters the membrane threshold potential and promotes a general change in the overall excitability of the stimulated tissue, this study shows that a decrease in the global neural excitability in a specific area of cortex, resulting from cathodal tDCS, combined simultaneously with PAS increases synaptic efficacy and induces synaptic plasticity in a short time period and to a greater degree than either protocol alone. There are clearly complex effects of the interaction once longer PAS protocols are used, as indicated by the finding that longer
PAS in conjunction with anodal tDCS produces lasting decreases in excitability (Nitsche et al., 2007).

In a 2011 study by Hasan and colleagues, tDCS was used to alter the plasticity in the human motor cortex induced by a special type of repetitive transcranial magnetic stimulation [rTMS] called theta-burst stimulation [TBS]. TBS has been found to produce significant and long-lasting neural effects by the use of short, low-intensity bursts of stimulation delivered at the theta frequency (~5Hz) (Huang et al., 2005; Huang et al., 2010). There are two specific protocols of TBS, each inducing a different effect on neural activity. Intermittent pattern TBS (iTBS) is known to enhance the amplitude of MEPs, while continuous TBS (cTBS) is known to suppress MEPs (Hasan et al., 2011; Huang et al., 2005; Huang et al., 2010). To test how tDCS alters plasticity, healthy subjects received either iTBS or cTBS stimulation of the motor cortex for time periods that were not previously found to have any lasting effect on neural activity. They then concurrently stimulated subjects using tDCS, but with an intensity and time course that had also been previously found to be insufficient to induce lasting effects on neural activity. Cross-matching stimulation protocols, iTBS or cTBS with cathodal tDCS or anodal tDCS, they were able to determine whether pairing TBS and tDCS stimulation could alter neural activity in a situation where neither type of stimulation had previously been shown to induce changes on its own. Using paired pulses of TMS to induce short interval cortical inhibition [SICI] and intracortical facilitation [ICF], they measured the induced changes in excitability of motor cortex (changes in amplitude of MEPs) over a time course of 30 minutes after stimulation. They found that iTBS with sham tDCS and iTBS with anodal
tDCS stimulation slightly enhanced MEP amplitude to a similar degree; however, iTBS with cathodal tDCS stimulation produced significantly higher MEP amplitudes. Interestingly, although cTBS with sham tDCS stimulation showed an expected slight decrease in MEP amplitude, cTBS with cathodal tDCS stimulation showed an increase in MEP amplitude and cTBS with anodal tDCS stimulation showed an even greater increase in MEP amplitude (Hasan et al., 2012).

It might be assumed that cTBS with cathodal tDCS stimulation would combine to have a greater inhibitory effect and lower MEP amplitudes; however, the exact opposite was observed. Similarly, it would be expected that iTBS with anodal tDCS stimulation might be more effective at increasing MEP amplitude than iTBS with cathodal tDCS stimulation, but this is not the case (Hasan et al., 2011). As in the studies examining the interaction with tDCS and PAS-induced neuroplasticity, the combination of tDCS and TBS suggest produces complex findings incompatible with the simple idea that tDCS simply increases or decreases excitability.

**THE EFFECTS OF CHANGING THE TIMING OF tDCS:**

In 2010, to investigate how changes in timing affects plasticity, Fricke and colleagues studied how changes in the duration of tDCS and the duration between two subsequent tDCS sessions affected the excitability in human motor cortex. Using previously established protocols (Nitsche & Paulus, 2000), they stimulated motor cortex in healthy subjects with 1mA of either anodal or cathodal tDCS and recorded MEP amplitudes. They confirmed previous findings (Nitsche et al., 2007) and demonstrated 5
to 10 minutes of anodal tDCS resulted in 5 to 30 minutes of increased excitability, while cathodal tDCS decreased excitability for a similar duration. However, when two 5 minute anodal tDCS sessions were interrupted by a 3 minute break, an initial increase in MEP amplitude quickly reversed after the first few minutes to an amplitude below the baseline average and persisted for 30 minutes. A similar reversal of effect was observed if two 5 minute sessions of cathodal tDCS were interrupted by a 3 minute break. If the 3 minute break between tDCS sessions was increased to 30 minutes, no reversal in effect was observed and the resulting after-effects were similar to the effects induced by a single tDCS session. Despite the reversal in effect, no difference in intracortical inhibition or facilitation was observed between a single 5 minute tDCS session and two sessions interrupted by a 3 minute break. These findings suggest that the duration of tDCS and the time period directly following influence the excitability of the cell.

The timing of tDCS is important for producing changes in excitability and also somewhat complex. More specifically, the total duration of stimulation and any interruptions between multiple stimulation sessions alters the effects observed (Fricke et al., 2010; Monte-Silva et al., 2012). Continuous anodal stimulation for a duration up to 13 minutes results in increased excitation for up to an hour (Monte-Silva et al., 2012; Nitsche et al., 2003); however, at some point between 13 and 26 minutes of continuous stimulation the effects are reverse and a decrease in excitability is observed (Monte-Silva et al 2012). Other studies using 20 minutes of continuous anodal stimulation observed positive enhancement in motor skill acquisition (Reis et al., 2009), suggesting that this critical switching of effect might occur sometime between 20 and 26 minutes of
continuous stimulation. Furthermore, some studies involving neurological diseases and disorders (discussed in later sections) used stimulation durations of 30 minutes or longer and found functional improvements that suggest no switching of effect.

Long interruptions of 3 to 24 hours between two anodal tDCS sessions of 13 minutes induce the opposite effect of a single 13 minute anodal tDCS session. Short interruptions of 3 to 20 minutes between two 13 minute anodal tDCS sessions are shown to delay the excitatory effects for several hours (Monte-Silva et al 2012). Short interruptions of a few minutes between two 5 minute anodal or cathodal tDCS sessions, are shown to induce the opposite effect observed in a single 5 minutes session. However, if the interruption duration is increased to 30 minutes, no change in effect is observed (Fricke et al., 2011).

The variance of neural activity in response to changes in duration and interruption between tDCS session is due to the complexity of plasticity. Because of this complexity and the poor state of knowledge regarding the mechanism of tDCS, most investigations involving the treatment of neurological diseases and disorders will typically treat subjects with single sessions of tDCS for durations under 26 minutes with intervals between sessions ranging from a few hours to days (see later sections on the use of tDCS to treat neurological diseases and disorders).

**PHARMACOLOGICAL STUDIES OF tDCS:**

In a 2012 study, Monte-Silva and colleagues used systemic pharmacological intervention to investigate plasticity induced by tDCS. They (and others) termed the
plasticity induced by tDCS LTP-like to separate it from the frequency-based LTP studied in animal work. Monte-Silva made a clear distinction between early [e-LTP] and late LTP [l-LTP] phases by characterizing late effects as excitability alterations lasting more than 3 hours. They claim that while single session stimulation is sufficient for e-LTP, two or more sessions within 30 minutes of each other are necessary to induce l-LTP. Other studies suggest that inducing prolonged excitability changes may be more complicated, involving complex timing and intensity of stimulation (Hasan et al., 2012; Fricke et al., 2010). Monte-Silva and colleagues first investigated the aftereffects of tDCS without pharmacological intervention. They applied 1mA of anodal tDCS to healthy subjects for 13 continuous minutes [13-0-0], 26 continuous minutes [13-0-13], and 26 minutes with a 3 minute [13-3-13], 20 minute [13-20-13], 3 hour [13-3hr-13] or 24 hour [13-24hr-13] break. They then recorded evoked MEP amplitude for the 120 minutes following the final tDCS session, and again later the same evening, the next morning, the next afternoon, and the next evening. They found that 13 minutes of continuous stimulation increased MEP amplitude for the following 60 minutes; conversely, 26 minutes of continuous stimulation decreased MEP amplitude for at least 60 minutes. With short interruptions of 3 or 20 minutes between tDCS sessions, only slight insignificant MEP elevation occurred for the first 120 minutes after the last tDCS session; however, a significant increase in MEP amplitude was noticed later that same day and continued until the next evening. Interestingly, waiting 3 hours or 24 hours between tDCS sessions resulted in a decrease in excitability, lasting up to 60 minutes after the final tDCS session.
Next, pharmacological intervention was used to determine if aftereffects were altered by blocking specific synaptic actions. First, flunarizine [FLU], a calcium channel antagonist, was used to block the entry of calcium. After applying 26 continuous minutes of anodal tDCS, which previous resulted in a decrease in evoked MEP amplitude lasting up to 60 minutes, they observed a complete abolition of this aftereffect in subjects given FLU, recording MEP amplitudes near baseline values. Next, dextromethorphan [DMO], an NMDA receptor antagonist, was administered. Using the 13-20-13 protocol that previously resulted in a later onset of excitability enhancement; they noticed that subjects treated with DMO did not experience this enhancement. The lack of aftereffect from tDCS observed after treating patients with FLU and DMO suggested that the sodium and calcium channels were involved in the mechanism of tDCS (Monte-Silva et al., 2012).

As found in previous a previous study (Fricke et al., 2010), Monte-Silva and colleagues showed that the interval between tDCS sessions and the duration of stimulation are key factors for inducing aftereffects. While they did observe changes in excitability, or lack thereof, after treatment with FLU and DMO, it is important to note that the precise location of action of FLU and DMO cannot be directed with any specificity to location and alter the excitability of the central nervous system in a widespread manner. Thus, the observed results may not be completely indicative of the precise mechanism of tDCS.

It seems clear that tDCS causes changes in neuronal excitation, but a mechanism by which tDCS produces this change cannot be identified with the current state of
investigation (Nitsche et al., 2003). Determining the complete extent of effects caused by the use of tDCS on locations near and far from electrode placement also remains unclear; specifically the effect of tDCS on subcortical populations. Neuronal activity is typically monitored in areas very superficial to the stimulating electrode, although changes have been reported in locations far deeper from the area of electrode placement, in areas of the central brain (DaSilva et al., 2012). It is very possible that the effects observed in deeper structures are the result of modulation in more superficial areas due to cortical and subcortical connectivity.

**OTHER FACTORS AND VARIABLES IN tDCS**

The direction of the tDCS effect depends on electrode polarity – placing the cathode over the region of interest will generally reduce excitability, and anodal stimulation will largely enhance excitability. Increasing the current intensity will increase the effect size, but weak currents are typically used to avoid the possibility of producing irritation of the skin. As seen above, the duration of stimulation can alter the effects of tDCS in unpredictable ways.

The neural effects of the tDCS are also likely tied to the architecture of the brain. The cortical layers closest to the active electrode experience the largest electrical field and the field decays with distance. However, it is important to note that the gyrification of the cerebrum is likely to alter the flow of the current in unpredictable ways, as is the changing boundary between brain tissue and the conducting CSF (Wagner et al., 2009; DaSilva et al., 2012).
While the method of studying tDCS has undergone a certain amount of standardization, confounding variables like age, gender, mood, stress level, and basal activation are not always given much attention. Many studies do analyze these variables if investigators believe there is a possibility of importance (e.g. handedness when recording unilaterally or gender in studies with asymmetrical disease prevalence). However, only a few of these studies provide statistical analysis to identify if these variables influence the result. Other variables that may influence the results in tDCS studies, such as temperature, blood-glucose, heart rate, and blood pressure, are typically not recorded at all. Temperature in particular has been shown to greatly influence neuronal activity during invasive procedures (Bindman et al., 1964), although temperature may be more stable during non-invasive studies.

**SUMMARY**

Despite the lack of clarity regarding the exact mechanism of action, transcranial direct current stimulation effectively alters cortical brain activity dependent on electrode placement, duration of stimulation, and the polarity and intensity of electrical current flow. The ability to enhance or inhibit the activity of specific cortical areas makes tDCS an ideal treatment for a wide range of neurological diseases and disorders.
APPLICATION OF tDCS FOR TREATMENT OF NEUROLOGICAL DISEASES
AND DISORDERS

STROKE:

Unlike the other neurological diseases and disorders commonly treated with tDCS, stroke is fundamentally different and more extensive in its definition, classifications, and prevalence. According to the World Health Organization [WHO], stroke is the loss or damage of brain tissue caused by an interruption in the cerebrovascular blood supply. It is the third leading cause of death in developed countries behind cancer and ischemic heart disease and is responsible for 9.7% of all deaths worldwide and 6.5% of deaths in the United States (Mathers et al., 2004; MacKay & Mensah, 2004). It is reported as the major cause of disability worldwide that consumes 2-4% of total healthcare costs (Donnan et al., 2007), and the total cost is estimated to be $73.7 billion in the United States in 2010 (Goldstein et al., 2010). Stroke is very likely the most prominent neurological disease being treated by tDCS.

The variance in location of blood supply interruption, severity, and type of stroke makes comparisons between recovery treatments very complex, which is essential to understand when evaluating the effectiveness of treatment with tDCS. Furthermore, unlike many neurodegenerative disorders, stroke has an acute onset and patients often see a recovery of brain function after the initial event that is typically classified into three stages: acute (within 7 days), sub-acute (2-3 weeks), and chronic (4-5 weeks or later) (Tohgi et al., 1990).
Ischemic and hemorrhagic stroke are the two major subtypes. Ischemic stroke occurs when blood flow is obstructed in the central nervous system, resulting in an inability to deliver nutrients and oxygen to brain tissue downstream from the obstruction. Prolonged ischemia results in cell death. Ischemic stroke is typically caused by a blood clot or narrowing of blood vessels and is by far the most common cause of stroke, accounting for approximately 85-87% of stroke cases (Lloyd-Jones et al., 2009; Go et al., 2012). Many clinicians and investigators make a distinction between symptomatic cerebral ischemic events that can last from a few minutes up to 24 hours [transient ischemic events - TIAs]; however, because the distinction between TIA and stroke is arbitrary no distinction will be made in this thesis (Donnan et al., 2007). Age, blood pressure, clinical findings, and the duration of symptoms are important when classifying stroke (Donnan et al., 2007). Ischemic stroke can be further divided into focal cerebral ischemia in which the blockage only affects a certain area of the brain, and global cerebral ischemia where ischemia is widespread throughout the entire central nervous system (often associated with cardiac arrest). Global cerebral ischemia is often investigated to identify neuronal populations more vulnerable to ischemia, which thus far includes neurons in the CA1 region of the hippocampus and specific populations of cells within the caudate, thalamus, neocortex and cerebellum (Back et al., 2004).

Hemorrhagic stroke accounts for approximately 13% of all stroke cases, and is characterized by blood vessel rupture, which can lead to an interruption of downstream blood flow (Go et al., 2012). Hemorrhagic stroke is further subdivided into intracerebral hemorrhage and subarachnoid hemorrhage. Approximately two-thirds of intracerebral
hemorrhagic strokes are the result of hypertensive small vessel disease, while the other third of cases typically occur as a result from abnormal formations of blood vessels called intracranial vascular malformations (cavernous angiomas or arteriovenous malformations [AVMs]). Subarachnoid hemorrhagic strokes are much less common (approximately 5% of all stroke incidences) and typically caused by the traumatic rupture of saccular aneurysms in the subarachnoid space (Donnan et al., 2007; Go et al., 2012).

Stroke is the result of a cascade of events. The initial point of blood flow interruption, and the immediate surrounding area, is typically referred to as the “core” and is the area of tissue most likely to experience irreversible damage and a high percentage of cell death. The tissue immediately downstream from the core is termed the “penumbra” and is the area most likely to experience mild to moderate ischemia and damaged tissue in this location has a higher probability of recovery. In most cases the core of the stroke receives less than 20% its normal blood flow while the penumbra will typically receive 20-40% of its normal blood flow. Reperfusion of affected tissue by blood within 30-60 minutes has been shown to significantly reduce infarct size in animal models; however, reperfusion after 6 hours is only believed to have a limited mitigating effect on the amount of tissue damage that develops (Sims & Muyderman, 2010). Intravenous thrombolytic treatment to return blood flow within 3 hours of symptom onset has shown to improve clinical outcomes at 3 months in patients with acute ischemic stroke (Lloyd-Jones et al., 2009). Interestingly, in 17% of ischemic stroke patients the spontaneous reversal of an arterial occlusion occurs within the first 6 hours and occurs in approximately 40-50% of stroke patients by the fourth day. Regardless of the type of
stroke, unless blood flow can be rapidly restored (within 5 minutes), the resulting ischemia will damage downstream tissues. This damage, often leading to cell death, is nonselective and will affect all cell types equally, including neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells in the brain (Sims & Muyderman, 2010).

**Mechanism of Pathology:**

From a histological standpoint, macroscopic and microscopic changes can be seen within 2-3 hours when neurons begin to shrink and scallop, vacuoles form in the dendrites, and a general swollen appearance of cells is observed. During these first few hours the extent of the damaged area may be difficult to demarcate. After approximately 12 hours of ischemia histological features that indicate irreversible damage may appear; these features include axonal swelling, eosinophilic neurons, and the occurrence of neuronal and astrocytic ghost cells (denucleated) (Back et al., 2004). This eosinophilia and denucleation are histological characteristics of apoptosis where DNA fragmentation, organelle swelling, and the release of intracellular contents occur, along with the formation of apoptotic bodies. Cells displaying apoptotic characteristics usually do not peak until 24 hours or more after the onset of the stroke. The cascade of events leading to cell death involves the mitochondria and mediation of the activation of caspases via an “intrinsic” or “extrinsic” pathway (Sims & Muyderman, 2010).

In the ischemic core, after blood flow is severely depressed, the metabolic balance is shifted. The Na+/K+ ATPase, which is responsible for maintaining the electrochemical
gradient conducive for the generation of action potentials [APs] and also for approximately 70% of total ATP consumption in the brain, is an important factor in creating this metabolic imbalance. Once the amount of oxygen becomes insufficient for aerobic metabolism, the ATP produced by the mitochondria is consumed within 2 minutes (Doyle et al., 2008). The concentration of glucose and ATP falls significantly in the first 5 minutes, although ATP ultimately stabilizes at 15-30% of its normal value for at least the first 2 hours. This stabilization may be due in part by creatine kinase, which is able to generate ATP from ADP using phosphocreatine (Sims & Muyderman, 2010). Eventually the lack of ATP causes the Na+/K+ ATPases on the plasma membrane to no longer be able to maintain the high concentration on intracellular potassium and extracellular sodium. This leads to neuronal membrane depolarization. Lack of ATP also prevents Ca++ ATPases from keeping low intracellular calcium levels. Increased calcium entry leads to activation of calcium-dependent proteases, lipases, and DNases, all of which are enzymes that can degrade cellular structure and lead to cell death if not constrained (Doyle et al., 2008).

Membrane depolarization, along with high levels of intracellular sodium, leads to neurotransmitter release, most notably the excitatory neurotransmitter glutamate. Increased entry of glutamate into the post-synaptic terminal leads to the activation of NMDA and AMPA receptors. NMDA receptors are of particular importance because they admit calcium, leading to greater depolarization and a higher calcium concentration, further adding to the excitotoxicity caused by a high concentration of intracellular
calcium. AMPA receptors have also been shown to admit calcium in a delayed manner when subjected to ischemia (Doyle et al., 2008; Mehta et al., 2007).

Peri-infarct depolarizations [PIDs] may be yet another occurrence following ischemia. Neurons in the penumbra have been observed that neurons in the penumbra become electrically silent for long periods of time following ischemia (Sims & Muyderman, 2010), and PIDs are the mechanisms of this depression. PIDs are defined as spontaneous depolarizations occurring in the penumbra that lead to spreading depression of electrical activity (Doyle et al., 2008; Mehta et al., 2007). PIDs are believed to be caused by the release of potassium, calcium, and excitatory amino acids (glutamate) by cells in the ischemic core, and the number of PIDs following stroke correlate with the size of the final infarct (Doyle et al., 2008; Back et al., 2004; Mehta et al., 2007), indicating that PIDs may expand the penumbra region.

Acidosis is another important consequence of ischemia. The lack of oxygen leads to the production of lactic acid following anaerobic glycolysis of glucose. ATP hydrolysis, without the regeneration of ATP, can also lead to acidosis. Moreover, the reduced blood flow allows acidic concentrations to increase (Sims & Muyderman, 2010). Acidosis also exacerbates calcium excitotoxicity via activation of acid-sensing ion channels [ASICs] by dissociated protons, which allow more calcium entry at specific pH sensitivities (Doyle et al., 2008).

Oxidative and Nitrative stress are also major factors that lead to cell death. The high levels of intracellular calcium, sodium, and ADP caused by ischemia lead to the
production of reactive oxygen species by the mitochondria. The increased levels of oxygen radicals lead to cell damage and activate signaling cascades that lead to apoptosis. Ischemia also results in increased levels of nitric oxide synthase [NOS] leading to increased levels of nitric oxide [NO] (a vasodilator), which eventually combines with superoxide to produce peroxynitrite, a powerful oxidant. The accumulation of NO, combined with the oxidative stress, also causes the over-activation of poly-ADP-ribose-polymerase 1 [PARP1], which is involved in DNA repair (Doyle et al., 2008). This over-activation of PARP1 leads to depletion of intracellular levels of NAD+, which is important in anaerobic glycolysis and mitochondrial respiration and the production of ATP (Doyle et al., 2008; Sims & Muyderman, 2010).

**Mechanism of Recovery:**

The events that facilitate recovery after stroke consist of many different processes, involving inflammation, cell recovery, and neuronal plasticity. While the inflammatory response of the immune system and the processes of cellular recovery play major roles in the recovery of brain tissue after stroke and vary according to the exact cause, the recovery that occurs after stroke of different areas is due not to the reversal of the process, but by the induction of adaptive neuroplastic mechanisms to re-route functions.

A hint about the mechanisms by which the brain could recover after stroke was gleaned from a 1990 investigation where increased stimulation of somatosensory receptors expanded the cortical representation of the stimulated area in adult owl monkeys (Jenkins et al., 1990). This suggested that cortical maps and organization was
not static, but modifiable. In 1991, Pons and colleagues found long-term somatosensory deafferentation (permanently severing the nerves that convey tactile sensation) in adult macaque monkeys led to the reorganization and “invasion” of adjacent cortical areas into the deafferented area. They also found that reorganization took place over a distance of up to 14 millimeters, significantly longer than the previously observed 1-2 millimeters from other short-term deafferentation investigations (Pons et al., 1991).

These “bottom-up” manipulations reflect the capacity for functional reorganization after elimination or alteration of input. Similar lines of thought applied to stroke require a “top-down” perspective. After stroke, the brain is attempting to manage the same functions after a loss of brain tissue, and recovery may reflect similar mechanisms of changes in map representations as seen in deafferentation studies.

In 1996 Nudo and his colleagues investigated the recovery of cortical motor function in squirrel monkeys after a surgically-induced ischemic infarct. They found that undamaged areas adjacent to the infarct underwent reorganization and appeared to take over the function of the damaged areas in monkeys that received training of the affected limb. In 2000, Liepert and colleagues supported these findings in humans when they observed increased number motor responses in the paretic hemisphere using TMS following constraint-induced training.

Treatments Options:

The complex nature of stroke has led to the development of many different recovery therapies and treatment options to regain function, including molecular
therapies (growth factors and other chemical messengers), stem cell transplantation, electromagnetic stimulation, device-brain stimulation, and physical therapy. While tissue lost in the core of the infarct is irreparable, the injured and sensitive tissue in the penumbra can recover and regain function. Typical acute treatments for ischemic stroke include administration of thrombolytic agents (e.g. recombinant tissue plasminogen activator [tPA]), aspirin, and decompressive surgery (Donnan et al., 2007). Glutamate antagonists are often used as a pharmacological blockade to stop the progression and occurrence of PIDs and have been found to improve deficits in animal studies (Back et al., 2004; Sims & Muyderman, 2010; Doyle et al., 2008). Most recovery occurs within the first three months after the onset of stroke, although late improvements are also occasionally seen (Cramer, 2008).

Physical therapy is the most common treatment of stroke after the subacute phase. There are many different types of physical therapy, which are roughly based on the principle that activation will improve motor and cognitive function by invoking neuroplastic mechanisms. Classical rehabilitation for stroke typically involves non-standardized physical and occupational therapy although many studies have investigated other therapies to treat stroke, including sensory based therapy, attention based therapy, mirror therapy, constraint-induced movement therapy [CIMT], and bilateral movement therapy. Sensory based therapies involve increasing or decreasing sensory (visual, attentional, kinesthetic) information to the patient in attempt to increase and focus cortical activation. Attention based therapies require the patient to provide feedback during training to maintain focus on rehabilitation. Mirror therapy uses mirrors to hide
the injured limb and create the illusion of perfect symmetry during motor tasks. In CIMT the healthy limb is constrained and the paretic limb is forced to complete motor tasks (Oujamaa et al., 2009). Bilateral arm training (with rhythmic auditory cues) requires subjects to engage in bilateral movements (Oujamaa et al., 2009; Luft et al., 2004). These approaches improve function by attempting to activate neurons and redistribute function to different regions. As a result, recovery from stroke largely depends on the neuroplasticity of the affected system. Since transcranial direct current stimulation produces this type of plasticity, it follows that it may have a role in accelerating this process.

Use of tDCS in Stroke:

The use of tDCS to treat stroke patients was first published in a 2005 study by Hummel and Cohen, who reported motor function improvement in an 84 year-old chronic stroke patient following a single 20 minute session of 1mA anodal tDCS. They placed the anodal electrode over the primary motor cortex of the lesioned hemisphere and the cathode over the contralateral supraorbital region. The goal of was to use anodal tDCS to increase the activity in motor cortex of the affected hemisphere by promoting neuroplasticity. They assessed his improvement before and after sham and active tDCS sessions using 3 measures of motor performance: the Jebsen-Taylor Hand Function Test [JTT] (used to measure motor skill), a pinch force task and a simple reaction time task. No motor improvement was seen after the sham session while significant motor improvement was seen after the tDCS session.
In a subsequent 2005 study, Hummel and his colleagues demonstrated in 6 chronic subcortical stroke patients that a single 20 minute (1mA) session of anodal tDCS to the ipsilesional motor cortex produced significant functional motor improvement. To become acclimated to the assessment procedure, the patients underwent 3 JTT assessments to establish a baseline performance. After a 30 minute break patients received either sham or anodal tDCS during another JTT assessment followed by two more JTT assessments 9 and 25 minutes after tDCS stimulation was terminated. The JTT assessments during and after tDCS all showed a modest, yet significant reduction of JTT time in all subjects compared to the control. After approximately 10 days, subjects returned for a final JTT assessment; however, no significant improvements remained (Hummel et al., 2005).

These early investigations showed that single-session unihemispheric tDCS resulted in a functional improvement of the affected upper extremity of chronic stroke patients, which was sustained even after the cessation of stimulation (Lindenberg et al., 2012). They did not, however, provide any evidence as to the change in neural activity that occurred to produce these functional motor improvements.

In 2005, Fregni and his colleagues used an almost identical study design as Hummel and his colleagues, with only one major addition; the application of cathodal tDCS to the unaffected (contralesional) hemisphere (motor cortex). This strategy was incorporated because of previous studies that suggested the contralesional cortex was disinhibited by the lesion. As a result, Fregni et al. postulated that reducing any such
hyperexcitability might improve function. They observed similar improvement in motor function from anodal stimulation of the affected (lesioned) hemisphere, but also found that cathodal stimulation of the unaffected hemisphere resulted in a significant improvement of motor function.

While single-session tDCS studies involving healthy individuals show that 1mA anodal stimulation durations of 10-13 minutes elicit aftereffects lasting up to an hour or longer (Monte-Silva et al., 2012; Fricke et al., 2011), the aftereffects of a single session of tDCS have not been found to last longer than a few hours in healthy subjects regardless of polarity (anodal or cathodal). Only repetitive tDCS stimulations interrupted with a short interval between 3 and 20 minutes have been shown to produce aftereffects lasting more than 24 hours (Monte-Silva et al., 2012). However, a 2012 study involving stroke patients found that a single 20 minute session of cathodal tDCS of 1mA applied over the contralesional primary motor cortex produced a significant functional improvement that lasted for at least 24 hours. This same study found that short interval intracortical inhibition [SICI] increased after tDCS in contralesional motor cortex while the lesioned motor cortex experienced a decrease in SICI, and although MEP amplitudes were found to be reduced (inhibited) when evoked from contralesional motor cortex, no changes were seen in MEP amplitude evoked from lesioned motor cortex (Zimerman et al., 2012). This suggests functional changes may be more complex and longer-lasting than physiological changes, and may or may not be exclusive to subjects with unilateral cerebral damage. The prolonged duration of aftereffects may be due to the combination of motor task training and tDCS.
Despite this recent finding of longer-lasting changes in stroke patients, due to the typical lack of sustainability in the aftereffects produced by single-session tDCS many investigations use multiple-sessions of tDCS, often combined with other types of stimulation (e.g. TMS, TBS or PAS), to elicit stronger and longer-lasting effects (Monte-Silva et al., 2012; Nitsche et al., 2007; Hasan et al., 2011; Fricke et al., 2010). Other findings have encouraged investigations to implement bihemispheric stimulation in stroke therapies (Murase et al., 2004; Lindberg et al., 2012).

The concept of bihemispheric stimulation developed from a 2004 neurophysiological study by Murase and his colleagues who investigated the interaction between the lesioned (ipsilesional) hemisphere and the intact (contralesional) hemisphere. Using a reaction time paradigm they measured and compared the interhemispheric inhibition [IHI] of the intact hemisphere with the lesioned hemisphere. Using TMS to elicit MEPs, they gave stroke patients and healthy individuals a conditioning stimulus followed 10 milliseconds later by a test stimulus. They then tested the reaction time of stroke patients (paretic hand) and healthy subjects (right hand) to make a voluntary movement following a “go” signal while measuring the electromyogram response. During the interval between the “go” signal and the voluntary response, a test stimulus (always to the hemisphere of the contralateral hand) was given at differing timing intervals to evaluate how it changed the resulting MEP. By measuring the difference between the MEP amplitude of the control responses and the voluntary reaction responses interrupted with a test stimulus they were able to measure the amount of inhibition that resulted from the timing changes of the interrupting test stimuli. In all subjects a peak of
inhibition was observed when the test stimulus was given at a certain point time before the onset of movement; however, in healthy subjects, stimulation occurring closer to the onset of movement eventually became facilitative while stimulation remained inhibitory in stroke patients regardless of proximity to movement onset. This finding of increased inhibition of the lesioned hemisphere motor cortex in stroke patients strongly suggests that the recovery of motor function following a stroke is affected by the balance of activity between the ipsilesional and contralesional hemisphere (most likely via the corpus callosum). The discovery of this imbalance led to subsequent tDCS investigations involving bihemispheric stimulation of stroke patients (Murase et al., 2004; Lindenberg et al., 2012).

Single-session 1mA anodal tDCS, with the anodal electrode placed over primary motor cortex and the cathodal electrode placed over the contralateral right orbit, was found to reverse its effect on neuronal activity from excitatory to inhibitory when applied for a duration of 26 minutes in an investigation using healthy subjects (Monte-Silva et al., 2012). However, in 2010 and 2012 investigations by Lindenberg and his colleagues tDCS was applied to the motor cortex of chronic stroke patients for 30 minutes at a current of 1.5mA with the anodal electrode placed over the ipsilesional motor cortex and the cathodal electrode placed over the contralesional motor cortex. The effect of this prolonged stimulation duration and high current intensity on neuronal activity was not measured in either study although functional motor improvements were observed that lasted up to a week after treatment (Lindenberg et al., 2010; Lindenberg et al., 2012). The improvement in motor function suggests that the ipsilesional cortex was upregulated.
while contralesional cortex was inhibited. Also, it appears that 30 minutes of anodal stimulation at 1.5mA did not cause a reversal of effect from excitatory to inhibitory as might be suspected from the 2012 Monte-Silva study. It is possible that the current density applied during stimulation is not concentrated enough to cause the reversal seen in other experiments due to the change in placement of the electrodes; nevertheless, other factors may also be involved (the cause of the reversal is unknown and also without measuring the neuronal activity is impossible to know the effect of stimulation on the areas stimulated).

In summary, current evidence supports the hypothesis that tDCS improves stroke deficits by although decreasing activity in the contralesional hemisphere and increasing activity in lesioned hemisphere. The studies reviewed in this thesis focus primarily on motor function, stimulating primary motor cortex, so it is not possible to comment on the effects of tDCS in regards to other cognitive functions, such as language comprehension and production. Furthermore, none of the studies reviewed provide direct evidence of the physiological changes in cortex that may help to establish the mechanism behind the observed functional improvements. Finally, the long-term efficacy of tDCS (greater than a few weeks) remains unexplored.

**PARKINSON’S DISEASE:**

In 1817 Parkinson’s disease [PD] was first described in detail by James Parkinson when he punctiliously described involuntary tremulous motion in his essay on the “shaking palsy” (Parkinson, 2002). In 1919 it was discovered that PD resulted from the
loss of cells in the substantia nigra, and in 1957 dopamine [DA] was identified as the neurotransmitter lost in PD by Carlsson and colleagues (Jankovic, 2007). In 1960 Ehringer and Hornykiewicz published their study and showed that a significant loss of DA occurred in the caudate nucleus and putamen of PD patients (Hornykiewicz, 2010). Shortly thereafter, in 1961, levodopa was first used in the treatment of PD to relieve bradykinesia (Jankovic, 2007; Hornykiewicz, 2010).

There are several important distinctions in the classification of PD. Parkinson’s disease or primary Parkinsonism, often likened to “paralysis agitans,” is characterized by a specific pathology and set of symptoms that are not attributable to another known neurological disease or disorder. While there are a small percentage of cases attributable to genetic and other factors, PD is typically “idiopathic,” or of an unknown cause. Secondary Parkinsonism, often referred to simply as Parkinsonism, is characterized by the presentation of movement abnormalities and symptoms commonly specific to PD where another disease or disorder is implicated (Hoehn & Yahr, 1967, Dauer & Przedborski, 2003).

Clinically, PD is identified by its four cardinal motor symptoms: resting tremor, rigidity, bradykinesia, and postural instability. Flexed posture, motor freezing, shuffling-gait, and slowing of certain activities are also commonly seen in patients with PD, as well as non-motor symptoms such as cognitive impairment, bradyphrenia, depression, apathy, fatigue, dysautonomia, sleep disorders, and various sensory symptoms like anosmia and pain (Jankovic, 2007). The clinical manifestation of PD is preceded by an insidious pre-
symptomatic phase during which the gradual loss of mesencephalic dopaminergic neurons occurs. Eventually unilateral symptoms appear that will develop bilaterally over time (Marek et al., 1996).

Parkinson’s disease is clinically divided into 5 stages. The time spent on each stage varies, especially with the beginning stages (stages 1-3) (Hoehn & Yahr, 1967; Shulman et al., 2008). The primary motor symptoms begin after the degeneration of 80% or more of the substantia nigra (Dauer & Przedborski, 2003) and mark the beginning of stage 1, which is characterized by slight tremors and inconveniences in daily activities. During stage 2, symptoms become bilateral, affecting both the left and right sides of the body, and the patient usually has difficult walking or maintaining balance; patients lose the ability to perform normal physical tasks. Stage 3 is characterized by severe motor dysfunction, where the patient may have lost the ability to stand or walk. There is also a noticeable slowing of movements. Stage 4 symptoms include bradykinesia and the loss of performing daily tasks. Patients may retain a slight ability to walk, and in some cases the severity of tremors decreases. Stage 5 is characterized by the inability of the patient to perform all daily tasks. They usually lose all ability to stand, walk, and perform most other simple physical movements; they must be under constant care (Shulman et al., 2008).

It is estimated that the incidence rate of PD in developed countries is 14 per 100,000 person-years. When restricted to individuals above the age of 65 the incidence increases to 160 per 100,000 person years. This predicts that approximately 60, 000
individuals will be diagnosed with PD every year (Wirdefeldt et al., 2011). It is currently estimated to affect 1 million people in the United States (Kordower & Bjorklund, 2013).

**Mechanism of Pathology:**

The primary pathological defect that causes Parkinson’s disease is a high percentage of dopaminergic cell death in the substantia nigra, principally the ventral portion of the pars compacta (Rubins et al., 2012; Davies, 2008). The resulting denervation of dopaminergic inputs from this area results in a wide range of defects. There are many events that may lead to the neuronal loss associated with Parkinsonism, including genetic and environmental factors; however, the pathological hallmark in PD is the development and presence of abnormal aggregates of alpha-synuclein-immunoreactive inclusions with neurofilament and proteolytic proteins. These aggregates appear as thread-like Lewy neurites [LNs] in cellular processes and Lewy bodies [LBs] in neuronal somata. Proteins often involved in LB/LN formation include alpha-synuclein, ubiquitin, neurofilaments, parkin, and synphilin-1 (Davies, 2008).

The progression of Parkinson’s disease is separated anatomically and histologically into 6 stages. The first two stages are asymptomatic and thus difficult to identify clinically. Stage 1 is characterized by the development of LNs and LBs in anterior olfactory structures and the dorsal motor nucleus of the vagus nerve. In stage 2 LN/LBs develop in portions of lower raphe nuclei (notably the great raphe nucleus) and magnocellular portions of the reticular formation. LNs may also be found in the noradrenergic neurons of the locus coeruleus. During stages 1 and 2, changes are
typically restricted to these specific areas of the medulla oblongata and pontine tegmentum. In stages 3-6 patients become symptomatic. While the cerebral cortex is uninvolved in stage 3, damage progresses to the central subnucleus of the amygdala, the cholinergic magnocellular nuclei of the basal forebrain, and the pedunculopontine nucleus [PPN]. LNs start to appear in the posterolateral subnucleus of the SNc. LBs, punctate structures, and pale bodies may also begin to appear in the melanin-laden projection neurons of the SNc; however, neuronal loss is not typical. In stages 4-6, damage spreads to other cortical and subcortical areas and significant neuronal loss occurs in the SNc (Braak et al., 2006).

The motor symptoms, which are the most iconic identifying symptom of PD, result from a lack of dopaminergic input to the striatum of the basal ganglia [BG], an important part of a motor association circuit. Certain areas of the striatum, which are innervated by the dopaminergic neurons of the substantia nigra pars compacta [SNc], no longer receive sufficient dopaminergic input when those cells are lost. The striatum also receives input from almost all areas of the neocortex, as well as certain thalamic nuclei. One area of the striatum, the putamen, contains neuronal populations that are characterized by the presence of either D1- or D2-type dopamine receptors. The neurons of the putamen containing D1-type receptors are part of the “direct” pathway of the BG circuit and project to the internal segment of the globus pallidus [GPi] and the substantia nigra pars reticulata [SNr] with inhibitory GABAergic input. Neurons in the putamen containing D2-type receptors are part of the “indirect” pathway (Alexander & Crutcher, 1990; Rubin et al., 2012). These neurons provide GABAergic input to the external
segment of the globus pallidus [GPe], which then projects GABAergic input to the subthalamic nucleus [STN] and GPi. The STN, which also receives excitatory glutamatergic input from cortex and the PPN, projects glutamatergic input to the GPi and SNr and back to the GPe. In summary, GPi and SNr receive inhibitory GABAergic input via the direct pathway and via the GPe of the indirect pathway, but also excitatory glutamatergic input via the STN of the indirect pathway. Overall, the thalamus (more specifically the anterior portion of the ventrolateral nucleus [VLa], the ventral anterior nucleus, and the centromedian nucleus [CM]) receives a tonic, GABAergic effect from the GPi and SNr, which is then relayed back to cortical areas (Alexander & Crutcher 1990, Rubin et al 2012).

**Figure 1: Basal Ganglia Circuit Diagrams.** Darker arrows represent excitatory input while lighter arrows represent inhibitory input. Figure take from Rubin et al., 2012.

Significant (50-60%) neuronal loss in the SNc eventually leads to significant loss of dopamine in the striatum (80-85%), at which point the symptoms of PD will appear (Wirdefeldt et al., 2011). This leads to altered activity in both the direct and indirect pathways.
pathways of the BG. The putamen exhibits lowered inhibitory control over the GPi via the direct pathway and increased inhibition of the GPe via the indirect pathway. The STN, receiving less inhibitory input via the GPe, increases its excitatory input to the GPi. The lack of inhibitory input from the direct pathway and the increase in excitatory input from the indirect pathway leads to increased activation of the GPi, which increases its inhibitory effect on its target nuclei in the thalamus and the PPN. This lowers the excitatory output from the thalamic nuclei to their respective cortical targets, leading to decreased activity in cortex (Rubin et al., 2012).

**Mechanisms of Recovery:**

The primary pathology of PD is the formation of LBs and LNs and the eventual loss of neurons in specific neuronal populations, most notably the substantia nigra par compacta. Evidence suggests that dysfunction of the ubiquitin-proteasome system [UPS] and the autophagy-lysosome pathway [ALP] may be key components of the neurodegeneration that leads to PD, and other neurological disorders. Failure of the UPS to properly remove misfolded or damaged proteins is associated with their intracellular accumulation and subsequently may be involved in the pathogenesis of PD. In fact, several genes related to PD (α-synuclein, parkin, and UCH-L1) are associated with the UPS. Similarly, failure of the ALP to properly remove intracellular content, particularly α-synuclein, is also implicated in the pathogenesis of PD. It is believed that enhancement of the UPS and ALP by small molecule enhancers [SMER] or other agents may help protect against PD or, at the very least, slow its progression (Pan et al., 2008).
New studies suggest that neurotrophic factors, which are known to have neuroprotectant qualities, may be able to aid in the prevention and recovery of PD. This family of proteins protects against cytotoxic cell damage and is shown to have antioxidant and antiapoptotic qualities. The use of glial cell line derived neurotrophic factor [GDNF] in animal studies and open-design clinical trials enhanced motor function, although blinded studies are needed for conclusions can be made (Kordower & Bjorklund, 2013).

**Treatment Options:**

One of the more successful drugs for treating Parkinson’s disease has been levodopa. Since dopamine cannot cross the blood brain barrier, levodopa, its precursor, is used. Levodopa is typically combined with carbidopa in order to prevent conversion of levodopa to dopamine before it reaches the brain. This is done through an enzyme known as dopa decarboxylase. Thus, carbidopa increases the availability of levodopa in the brain and decreases the adverse side effects of dopamine such as nausea and hypotension. The most widely prescribed medicine that uses a slow release dosage combination of levodopa and carbidopa is Sinemet (Rao et al., 2006).

Levodopa is particularly effective at limiting bradykinesia and rigidity, but is less effective in correcting speech, postural reflex and gait disturbance. Levodopa does not slow down the rate of loss in dopaminergic neurons and over time becomes less effective as patient tolerance to the medication increases (Fischbach & McKhann, 2001). Entacapone has been shown to enhance levodopa absorption and improve motor
symptoms. It must have bimodal delivery and works by inhibiting catechol-O-methyltransferase [COMT] which enhances absorption and decreases PD “off” time. Entacapone increases the half-life of levodopa through the inhibition of COMT which is responsible for the degradation of Levodopa to 3-O-methylldopa [3OM]. This causes less levodopa to be absorbed by the intestines and increases its availability. The bimodal administration of entacapone was shown to be the key in increasing the effectiveness of levodopa and increasing its half-life. The best bimodal timing was 1 hour (Bet et al., 2007).

Examples of dopamine agonists include pramipexole and ropinirole. A hybrid treatment with dopamine agonists and Levodopa yields good results as it reduces the motor complications associated with the use of dopamine agonists. Another common agent used for treatment is the Monoamine Oxidase [MAO]-B inhibitor. By inhibiting the activity of MAO, MAO-B inhibitors prevent the breakdown of monoamine neurotransmitters (primarily dopamine and phenethylamine) (Bet et al., 2007).

It was believed that the adenosine receptor [A2AR] antagonists may help the motor and neuroprotective effects of certain cells in the brain of PD model mice (known as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] mice). It was found that A2AR activity in forebrain neurons is critical to the control of motor activity, while brain cells (likely glial cells) in other areas are important components for protection against acute MPTP toxicity. The adenosine receptors are key components in the degeneration of
dopaminergic neurons. Blockage of these receptors also blocks the degenerative effects and alleviates the loss of dopaminergic cells and motor deficits (Yu et al., 2007).

The implantation of a deep brain stimulator [DBS] and cell transplantation are also possible treatments for Parkinson’s disease. In transplant studies, fetal dopamine cells are transplanted unilaterally or bilaterally to areas of the striatum (caudate and putamen). Long-term improvements are observed in many patients who undergo transplantation surgery (Freed et al., 1992; Spencer et al., 1992). DBS has also shown long-term improvement in patients; stimulation of the subthalamic nucleus [STN] and globus pallidus internus [GPI] has proven to be the most effective (Fasano et al., 2012). Despite the positive results seen in some patients, the risk associated with neurosurgery makes these treatments less favorable than non-invasive treatments.

**Use of tDCS as Treatment:**

Transcranial direct current stimulation is non-invasive, safe, and causes very few side effects, if any, unlike other treatments for PD such as medication or surgery. It is easy to perform and requires less expensive equipment than other non-invasive treatments like TMS. Penetrance of transcranial direct current is believed to be rather limited and there is no evidence that supports the effects of tDCS are capable of directly targeting subcortical structures like the basal ganglia (Fregni et al., 2006b). Thus, tDCS most likely acts to improve PD symptoms via secondary effects.

In 2006, Fregni and colleagues were the first to study the effects of tDCS on patients with idiopathic PD. The first group of patients received 20 minutes of 1mA
anodal tDCS followed by 20 minutes of sham tDCS 48 hours later. Electrodes were placed over primary motor cortex and the contralateral supraorbital area. The second group received the same protocol except with cathodal stimulation. A third group underwent the same protocol as the first group except the anodal electrode was placed over the dorsolateral prefrontal cortex [DLPFC]. All patients received tDCS to the dominant hemisphere regardless of any bilateral differences and were required to not take any medication for at least 12 hours leading up to the experiment. The investigators assessed functional motor improvement immediately following treatment using the Unified Parkinson’s Disease Rating Scale [UPDRS], simple reaction time [sRT], and Purdue Pegboard test [PPT]. They also measured changes in MEP amplitude in the first and second groups. They found that anodal tDCS of primary motor cortex resulted in a significant improvement of UPDRS and sRT. They also confirmed that MEP amplitude increases after anodal stimulation while it decreases following cathodal stimulation; however, only anodal stimulation also correlated with a positive motor function improvement. By using a secondary location (DLPFC) they were able to further confirm that specific electrode placement is necessary to generate a significant motor effect; however, stimulation to the DLPFC may still be beneficial to patients with PD in other regards to other areas of cognitive function. While the investigation successfully showed a positive motor improvement it did not provide any information regarding the duration of the effects produced.

Another 2006 study by Boggio and colleagues investigated working memory enhancement in patients with idiopathic PD following anodal tDCS of the left DLFPC.
Patients received 20 minutes of either 1mA or 2mA anodal tDCS followed by sham tDCS separated by at least 48 hours. Electrodes were placed over the left DLPFC and the contralateral supraorbital area. Subjects were assessed using a three-back memory test and were allowed to practice until they reach a stable performance plateau. As in the 2006 Fregni et al study, they used the same protocol except with the anodal electrode placed over primary motor cortex, which served as a control to determine if electrode placement was significant. They discovered that 2 mA, but not 1mA, of anodal tDCS of the DLPFC resulted in significant improvement in working memory. The duration of aftereffects was not investigated.

A 2010 study by Benninger and colleagues used a slightly more complex design to further investigate the use of tDCS in PD treatment. Active group patients received 20 minutes of 2mA anodal tDCS 8 times over the course of 2.5 weeks (Monday, Wednesday, Friday). The anodal electrode was moved between primary motor areas and prefrontal areas, alternating every other session so that each location was stimulated 4 times. The cathodal electrode was placed over the mastoid. Patients were further categorized into groups receiving tDCS while “on” medication and “off” medication. Assessments included measuring changes in walking time (gait) over a distance 10 meters and changes in bradykinesia by executing a motor sequence. Assessments were made before, 24 hours, 1 month, and 3 months after treatment. They found that anodal stimulation of both prefrontal areas and motor areas significantly improved bradykinesia for up to 3 months. They also noted gait improvement for shorter period in patients during the “off” period (Benninger et al., 2010).
At present, evidence regarding the use of tDCS in PD patients is positive although further investigation is needed to determine the long-term effects of tDCS as well as how the pathogenesis of the disorder relates to the mechanisms of action of the tDCS effects. Given the efficacy and mechanisms of DBS, it may be that transcranial stimulation produces effects by increasing the excitability of the motor (or other) cortex and compensates for the PD-induced attenuation of thalamocortical activity.

**ALZHEIMER’S DISEASE:**

In 1907 Alois Alzheimer published an article on the clinical and anatomical findings regarding the neurological impairment of a female patient. At age 51 she presented with a rather sudden loss of memory. Her symptoms included strange lapses in judgment, loss of episodic memory, disorientation, and the inability to recall certain words and phrases or recognize certain objects; however, her peripheral motor functions and reflexes appeared intact. Post-mortem anatomical investigation revealed abnormal changes to the thickness and appearance of intracellular neurofibrils, which were often found where neurons previously resided, and the deposition of a “special substance.” These two abnormalities were later identified as senile plaques [SPs] and neurofibrillary tangles [NFTs] (Stelzmann et al., 1995; Francis et al., 1999; LaFerla et al., 2007). In this patient, approximately 30% of all neurons of the cortex displayed these abnormal changes and changes were particularly noted in the upper layers of cortex (Alzheimer et al., 1995). Today patients presenting with similar clinical and post-mortem anatomical findings are diagnosed with Alzheimer’s disease [AD].
Alzheimer’s disease is the most common type of degenerative dementia and accounts for between 60-80% of all dementia cases. Approximately 1 in 8 Americans over the age of 65 will be diagnosed with AD, making it the 5th leading cause of death of individuals in that age group. Statistically women are more likely to develop AD; only a third of cases are men. In 2011 it was estimated that 5.4 million people suffer from AD in the United States with an annual cost estimated to be approximately $183 billion. Sadly, even more cost should be attributed to the treatment of AD and other dementias due to the high level of unpaid care by families. In 2010, almost 15 million people in the United States provided care for a person diagnosed with Alzheimer’s disease, valued at over $200 billion (Alzheimer’s Association Facts & Figures Report, 2011).

Dementia is defined as the abnormal degeneration of cognitive function that must include a decline in memory function and the decline of at least one other cognitive ability, such as language comprehension and generation, the ability to identify stimuli, the ability to plan and execute higher order tasks, and competent motor function. AD involves several common early clinical symptoms, including difficulty remembering recent events and general life details, apathy, and depression. Eventually patients may develop other symptoms, such as disorientation, impaired judgment, confusion, changes in behavior, and complications with speech, swallowing and walking. Histologically, the hallmark indicators for AD are the presence of β-amyloid plaques and neurofibrillary tangles [NFTs] of tau protein, as well as a decline in cholinergic function and the loss of specific neuronal populations (Alzheimer’s Association Facts & Figures Report, 2011;
Mechanism of Pathology:

Cognitive function degrades naturally over time and the cause is relatively unknown although oxidative stress, accumulation of neurotoxic aggregates, and many other factors may play a role. There are two pathological hallmarks for identifying AD: amyloid plaques and neurofibrillary tangles involving the tau protein (Morrissette et al., 2009; LaFerla et al., 2007, Ihara et al., 1986). Nonetheless, it is important to understand that even non-demented patients (identified using the Clinical Dementia Rating [CDR]) develop plaques and tangles over time. However, their distribution and progression differs markedly and are likely independent events (Price & Morris, 1999). Other significant pathological events also occur that may be involved in the development of AD, including inflammatory responses and oxidative stress (LaFerla et al., 2007, McGreer et al., 2006, Markesbery, 1997).

Amyloid plaques, which are comprised of oligomers of the neurotoxic 42-amino acid variant β-amyloid, are the result of improper cleavage of the amyloid precursor protein [APP] by either the beta-APP-cleaving-enzyme [BACE] or the γ-secretase enzymatic complex (Morissette et al., 2009). Although it was proposed that plaque numbers are directly related to cognitive decline in a quantitatively measurable way in the mid-1960s (Roth et al., 1967; Yankner & Lu, 2009), more recent studies proved the pathology was slightly more complex, involving formation of NFTs and synaptic loss.
(Yankner & Lu, 2009; Price & Morris, 1999). The core component in senile plaques was not identified as amyloid protein until the mid-1980s (Glenner & Wong, 1984; Masters et al., 1985). Later it was confirmed that amyloid β protein was neurotrophic at low concentrations and neurotoxic to differentiated mature neurons at high concentrations (Yankner et al., 1990).

Subsequently several genes, related to the formation and processing of amyloid proteins, were investigated for their involvement in the development of amyloid plaques. Although there are many genetic factors that play a role in both the familial and sporadic forms of AD, only a small percentage (<1%) of AD cases are considered genetically hereditary (Morrissette et al., 2009). Thus far, mutations in the genes encoding APP and presenilins 1 & 2 are associated with the familial form of AD (Morrissette et al., 2009; Yankner & Lu, 2009; Yanker et al., 1990; Goldgaber et al., 1987; Goate et al., 1991; Murrell et al., 1991; Rogaev et al., 1997). Furthermore, a higher number of apolipoprotein E type 4 allele [APOE-ε4] strongly correlates with an increased chance to develop AD and is common to both the familial and sporadic forms of the disease (Corder et al., 1993; Corder et al., 1995).

In non-demented brains tangles begin to be seen in many vulnerable areas after the sixth decade of life. This occurs preferentially in limbic structures and includes the perirhinal and entorhinal cortex, the anterior olfactory nucleus, and areas like the CA1 of the hippocampus. Typically, tangles are not present or very few in number in neocortex.
and Meynert nucleus. After age 70 the density of tangles appears to increase exponentially (Price & Morris, 1999).

While tangles are always present and develop in a specific pattern, plaques develop in a dissimilar pattern both spatially and temporally, appear more slowly and may even remain absent until a very late age. While the presence of amyloid plaques does not appear to alter the pattern of tangle distribution, it may increase the rate of tangle formation (Price & Morris, 1999).

**Mechanisms of Recovery:**

Although much is known regarding the pathology of Alzheimer’s disease there is currently no evidence to support a mechanism of recovery or prevention (Daviglus et al., 2010). Predicated on the significance of areas like the locus coeruleus in the pathogenesis of AD, there are theories that suggest α-adrenergic agonists, β-adrenergic antagonists, and norepinephrine transport inhibitors may be able to limit the cognitive decline seen in patients (Jicha & Rents, 2013).

**Treatment Options:**

There is currently no effective treatment for Alzheimer’s disease. It is hypothesized that antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement may play a role in the prevention AD and help to hinder its progression (Daviglus et al., 2010).
Use of tDCS as Treatment:

As previously stated, tDCS has many positive attributes including ease of use, low cost, and a non-invasive safe protocol. Unlike in Parkinson’s disease, which is characterized by severe motor dysfunction that can be more easily measured and assessed, it is slightly more difficult to evaluate improvement in Alzheimer’s disease, which is characterized by memory dysfunction. Because of the evidence supporting a high level of neurodegeneration found in temporoparietal [TP] structures, many tDCS studies involving AD focus stimulation in these areas.

It appears Ferrucci and colleagues were the first to investigate the effectiveness of tDCS stimulation in patients with AD. They decided to use anodal, cathodal and sham tDCS to the TP area applied during three 15 minute sessions with a week between each session at an intensity of 1.5mA. The secondary electrode was placed on the deltoid. Each patient was assessed before and 30 minutes after each tDCS session using a word recognition task and visual attention task. They found that anodal stimulation significantly increased word recognition, while cathodal tDCS decreased word recognition. Sham tDCS was indifferent from baseline levels.

A 2008 study by Boggio and colleagues investigated the effect of tDCS on recognition, working memory, and selective attention in 10 patients with AD. Patients received 2 sessions of 2mA anodal tDCS for 30 minutes to either the left DLPFC or left temporal cortex, as well as a single session of sham tDCS. Sessions were separated by at least 48 hours. They assessed patients starting 10 minutes after stimulation onset until the
end of stimulation using the Stroop test (selective attention), the digit span test (working memory), and a visual recognition memory task (VRM). The results showed a significant improvement in visual recognition (VRM task) for both locations of stimulation, but no other significant improvements were seen from the other assessments (Boggio et al., 2008). Whether these effects lasted for any duration after tDCS cessation was not investigated.

Boggio and colleagues expanded their study design in a subsequent 2012 study to include multiple tDCS sessions and measure the impact of bilateral anodal stimulation of temporal areas. Patients received bilateral 2mA anodal stimulation for 30 minutes each day for 5 consecutive days. They also received sham tDCS following the same protocol. Patients were assessed using the mini-mental state exam [MMSE], Alzheimer Disease Assessment Scale-cognitive [ADAS-cog], a visual recognition task [VRT], and a visual attention task [VAT]. Assessments were taken before, directly after, 1 week after, and 4 weeks after treatment. The only significant effect was an improvement in the VRT that persisted for up to 4 weeks (Boggio et al., 2012).

The results of tDCS for the treatment of AD are very promising thus far, but only visual recognition improvements are considerably supported. There is hope that tDCS may be able to prevent the progression of AD or help susceptible neurons recover by modulating neuroprotective mechanisms that may help alleviate oxidative stress and regulate gene expression. It is likely that any identified tDCS effects are a result of
increasing neuronal excitability and countering impairments pursuant to intracellular aggregations of material.

**DEPRESSION:**

Unipolar depression, also known as major depressive disorder [MDD] or clinical depression, is the most common mental disorder worldwide. It is the leading contributor to disease burden in high income countries and ranks third in world, only surpassed by lower respiratory infections and diarrheal diseases. MDD is especially problematic for women; it is the leading cause of disease burden for women age 15-44 in low, middle, and high income countries (Mathers et al., 2008). In order to be diagnosed with MDD, patients must have experience two or more major depressive episodes, separated by at least two months. A major depressive episode requires the patient to experience at least five of the symptoms listed in Table 1 for at least 2 weeks. These symptoms must be present almost every day, cause significant impairment in daily life activities, and not attributable to substance abuse, a general medical condition, or normal mourning after a recent traumatic event (American Psychiatric Association, 2000).

**Table 1: MDD Depressive Episode Symptoms:**

<p>| | |</p>
<table>
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<tr>
<td>1.</td>
<td>Depressed mood (e.g. feeling sad, lonely, or unhappy) for a majority of the day.</td>
</tr>
<tr>
<td>2.</td>
<td>Apathy (severely diminished interest) or inability to find any pleasure in daily activities.</td>
</tr>
<tr>
<td>3.</td>
<td>Significant increase or decrease in appetite or unintentional weight-loss or weight gain.</td>
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<tr>
<td>4.</td>
<td>Insomnia or hypersomnia.</td>
</tr>
<tr>
<td>5.</td>
<td>Psychomotor agitation or retardation that is observable by a third party.</td>
</tr>
<tr>
<td>6.</td>
<td>Fatigue or loss of energy without an apparent cause.</td>
</tr>
<tr>
<td>7.</td>
<td>Feelings of excessive guilt or worthlessness.</td>
</tr>
<tr>
<td>8.</td>
<td>Diminished ability to think or concentrate, or indecisiveness.</td>
</tr>
<tr>
<td>9.</td>
<td>Recurrent thoughts of death or suicidal ideation.</td>
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Bipolar disorder, another common mood disorder, is often misdiagnosed as clinical depression (Willner et al., 2012; Marchand et al., 2013). In general in order to diagnose bipolar disorder patients must experience more than one bipolar episode, which includes both manic and depressive episodes. Depressive episodes must follow the same criteria mentioned previously while manic episodes are characterized by a distinct period of significantly elevated, expansive, or irritable mood, duration of at least 1 week, and the presence of at least three of the symptoms listed in Table 2.

**Table 2: Bipolar Disorder Manic Episode Symptoms:**

| 1. Increased self-esteem or grandiosity |
| 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep) |
| 3. More talkative than usual or pressure to keep talking |
| 4. Surge of ideas or subjective experience that thoughts are racing |
| 5. Easily distracted (i.e., attention too easily drawn to irrelevant external stimuli) |
| 6. Increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation. |
| 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences. |

There are three types of bipolar disorder: Bipolar 1 Disorder, Bipolar 2 Disorder, and Cyclothymic Disorder. In Bipolar 1 Disorder manic and depressive episodes cycle rapidly (daily), although mania is the primary mental state. Bipolar 2 Disorder recurrent depressive episodes are interrupted by hypomanic episodes. Cyclothymic Disorder is characterized by chronic cycling of hypomanic and depressive episodes that does not

Mechanism of Pathology:

While major depression and bipolar disorder most likely involve dysfunction in similar neural networks, direct evidence of this linkage remains absent. It is important to remember that bipolar disorder involves both manic and depressive episodes that may be caused by different pathologies.

One theory regarding the development of major depression involves the hypothalamus-pituitary-adrenal [HPA] axis, chronic stress, and a possible predisposition for depressed mood. An integral part of this theory is a cascade of HPA axis events that leads to glucocorticoid release. The release of corticotroping releasing hormone [CRH] from the paraventricular nucleus of the hypothalamus causes the release adrenocorticotropin hormone [ACTH] from the pituitary, which stimulates glucocorticoid (e.g. cortisol) release from the adrenal gland (Willner et al., 2012).

The HPA axis is regulated by many different inputs, although several areas are of particular interest, primarily the amygdala and hippocampus. There are several feedback loops implicated in the stress theory for depression. The amygdala, which is activated by emotion stimuli, exerts excitatory control over the HPA axis via the hypothalamus in an excitatory feedback loop. Conversely, the hippocampus acts as inhibitory negative feedback input to the HPA axis. Many areas of prefrontal and prelimbic cortex,
associated with the amygdala and hippocampus, are involved in the pathogenesis of depression (Willner et al., 2012).

Chronic exposure to glucocorticoids is neurotoxic and leads to the loss of glucocorticoid receptors in areas of feedback. It is also shown to increase activity of MAO-A (an enzyme responsible for degradation of monoaminergic neurotransmitters), leading to a decrease in serotonin and norepinephrine levels. While studies show that the hippocampus is vulnerable to glucocorticoid toxicity and impaired by prolonged exposure to stress, post-mortem analysis of hippocampal tissue samples in depressed patients who committed suicide revealed no observable loss of cells this particular area. Despite literature inconsistencies, there is believed to be morphological differences in certain regions of hippocampus in persons suffering from major depression.

Various areas of the prefrontal cortex are also believed to be damaged as a result of prolonged stress. This includes the left dorsolateral prefrontal cortex [DLPFC] where an elevated level of N-acetyl aspartic acid, a neurodegenerative indicator, is positively correlated with the duration of depression (Willner et al., 2012). Functional magnetic resonance [fMRI] and positron emission tomography [PET] imaging studies reveal a reduced metabolism (cerebral blood flow) in the left DLFPC and an increase in metabolism in the right DLFPC in patients with clinical depression (Grimm et al., 2008). Recent imaging studies by Marchand and colleagues provide evidence that strongly suggests dysfunction of cortico-basal ganglia circuitry is also involved in both unipolar depression and bipolar disorder, and may be the primary neuropathology in unipolar
depression (Marchand et al., 2010; Marchand et al., 2011; Marchand et al., 2012; Marchand et al., 2013).

Many other networks and areas are also implicated in the neuropathology of these two mood disorders. A group of functionally and anatomically related cortical midline structures that includes the dorsal medial prefrontal cortex [DMPFC], subcortical structures like the dorso-medial thalamus [DMT], ventral striatum [VS], supragenual anterior cingulate cortex [SACC] and precuneus have all demonstrated “self” related activity in neuroimaging studies. These same areas displayed abnormal neural activity in patients with unipolar depression. Interestingly, in a recent imaging study, the right posterior cingulate cortex [PCC] (an area of the limbic system), which has connections to the DMPFC, displayed functional activity that distinguished between patients with bipolar 2 disorder and unipolar depression. This suggests that the PCC may be a key differentiator between bipolar disorder and major depression neural activity (Grimm et al., 2009; Anand et al., 2009; Marchand et al., 2010; Marchand et al., 2011; Marchand et al., 2012; Marchand et al., 2013).

Another area of particular interest is the lateral habenula, which is responsible for mediating negative emotional response and believed to balance activity between the amygdala via serotonin and nucleus accumbens via dopamine. Over-activation of the lateral habenula was demonstrated in human and animal studies involving stress and depression. The major output of the lateral habenula is to the dorsal raphe nucleus [DRN], where it activates serotonergic cells during stressful events. A second major
output to the ventral tegmental area [VTA] causes inhibition of dopaminergic cells (Willner et al., 2012).

Many neurotransmitters are implicated in both major depression and bipolar disorder. In unipolar depression decreased dopamine is believed to play a major role; suspicions hint that a decrease in dopamine leads to a decrease in striatal activity (Bajbouj et al., 2006). In animal studies of anhedonia, the inability to experience pleasure, a decrease in the activity of dopaminergic projections to the nucleus accumbens from the VTA was demonstrated, which may be related to increases activity in the lateral habenula (Willner et al., 2012). Many other major neurotransmitters (glutamate, GABA, acetylcholine, norepinephrine, and serotonin) are also suspected to be involved in unipolar depression and bipolar disorder. A 2006 study by Bajbouj and colleagues observed differences in motor cortex activity elicited by TMS between subjects with MDD and healthy volunteers. They found abnormal asymmetry of the motor threshold between hemispheres, decreases in the cortical silent period following SICI, and decreased ICI in subjects with depression. These findings suggest a GABAergic tone deficiency associated with major depression (Bajbouj et al., 2006). Evidence of decreased volume and low levels of GABA in the anterior cingulate cortex [ACC] in patients with major depression also supports a GABA deficiency theory (Willner et al., 2012).
Figure 2: Possible Interactions Involved in Depression: Diagram shows how interplay of amygdala, hippocampus and associated areas in response to stress may lead to symptoms of depression. Figure taken from Willner et al., 2012.

Mechanisms of Recovery:

Recovery from depression is very complex and involves restoring balanced activity to areas associated with stress and emotion. Key areas associated with depression include the amygdala, hippocampus, caudate nucleus, nucleus accumbens, substantia nigra, lateral habenula, VTA, dorsolateral and ventromedial areas of prefrontal cortex, raphe nucleus, and the ACC. Increased excitation of the amygdala and areas like the lateral habenula, medial prefrontal cortex, and ventral and rostral ACC is associated with
depression. Contrarily, decreased activity in the hippocampus and areas like the raphe nucleus, left DLPFC, the VTA, caudate nucleus, and nucleus accumbens is also associated with depression. Many of these areas influence each other and contribute to depression in varying degrees.

**Treatment Options:**

Many pharmacological medications are used to treat major depression, including MAO inhibitors, tricyclic antidepressants, selective reuptake inhibitors, and a host of other “atypical” antidepressants (Willner et al., 2012). Many of these drugs were first developed in the 1960s and 1970s. MAO inhibitors, which prevent the degradation of monoamine, were developed to correct deficiencies in monoaminergic (e.g. serotonin, norepinephrine, and dopamine) function (Wong et al., 2005).

In general tricyclic antidepressants work by amplifying serotonin and norepinephrine; however, lack of selectivity causes side effects (Willner et al., 2012). Perhaps the most famous medication for treating major depression is fluoxetine hydrochloride (Prozac), a selective serotonin-reuptake inhibitor [SSRI]. Although it was first developed in 1974, approval from the United States Food and Drug Administration did not come until 1987. By 2002, total sales reached $22 billion in the United States and 40 million patients had been prescribed worldwide (Wong et al., 2005). SSRIs work by increasing the concentration of neurotransmitters (e.g. serotonin in raphe nucleus and hippocampus). Other selective reuptake inhibitors are also effective and may work by preventing the reuptake of serotonin, norepinephrine, or both.
When medication proves unsuccessful, other treatments are often necessary. One of the oldest treatments for major depression is electroconvulsive therapy [ECT], which was first used approximately 75 years ago. ECT is used to treat patients with severe or drug-resistant depression and is essentially the application electrical current into the brain to induce seizures. The reasons behind its efficacy are largely unknown although theories regarding increases in neuroendocrine activation, monoamine neurotransmitter release, and seizure threshold are often discussed (Kellner et al., 2012). Deep Brain Stimulation [DBS] is another treatment option for patients with severe drug-resistant depression. DBS excitation of the nucleus accumbens and inhibition of lateral habenula are both possible treatments for major depression (Willner et al., 2012).

**Use of tDCS as Treatment:**

Most tDCS studies of depression focus on treating patients with MDD while very few use tDCS to treat patients with bipolar disorder (Brunoni et al., 2012). All tDCS investigations found while researching this thesis use tDCS to alter activity in the DLPFC, either unilaterally or bilaterally. The reasoning behind the attention to this particular area stems from the aforementioned imaging studies that observed asymmetrical activity in patients with MDD; hypoactivity in left DLFPC and hyperactivity in right DLFPC (Grimm et al., 2008).

In the 1960s and 1970s tDCS was used to treat patients with major depression although evidence to support its efficacy was mixed. In 2006, Fregni and colleagues were the first to use tDCS to treat MDD after more recent tDCS studies showed its
effectiveness at modulating neuronal activity (Nitsche et al., 2003; Fregni et al., 2006a). They studied the effects of tDCS in 18 right-handed patients with mild to moderate MDD after 5 alternate days of a single 20 minute session of 1mA anodal stimulation to the left DLPFC. The cathodal electrode was placed over the contralateral supraorbital area. All subjects did not take any antidepressant medications for at least 3 months prior to participation and were assigned to either a sham (control) or active treatment group. Using the Hamilton Depression Rating Scale [HDRS] to measure mood, a significant improvement was observed after the 5th day of treatment in patients receiving active stimulation compared to those receiving sham stimulation.

In 2007 Boggio and colleagues investigated the effects of tDCS applied to the left DLPFC compared to control group receiving tDCS to the occipital cortex. All 40 subjects were right-handed, diagnosed with mild to moderate MDD, and were not taking any antidepressant medications. Of the 40 subjects, 21 subjects received 20 minutes of active 2mA anodal stimulation to the left DLPFC each weekday for 2 weeks (total of 10 days); 9 subjects (active control) underwent the same protocol with anodal stimulation applied to the occipital cortex; and 10 subjects (placebo control) underwent the same protocol with sham stimulation. The reference electrode in each case was placed over the right supraorbital area. The HDRS and Beck Depression Inventory [BDI] were administered before treatment, immediately after, 15 days after, and 30 days after treatment in order to assess the mental state of each patient throughout the study. They found that anodal tDCS treatment of left DLFPC produces a significant reduction in the depression scores of patients with MDD that lasts for at least 30 days. Furthermore, they showed that the
observed results are specific to the area of stimulation since no significant change was seen between the placebo and active control groups.

Another 2008 study by Rigonatti and colleagues compared the effects induced by anodal tDCS to the left DLFPC to the treatment of depression with fluoxetine, an antidepressant medication in the selective serotonin reuptake inhibitor [SSRI] class. All patients had mild to moderate MDD and did not take any antidepressant medication for at least 2 months before the study. They were assed using HDRS and BDI before and 2, 4 and 6 weeks after the onset of treatment. Of the 42 patients, 21 received 20 minutes of 2mA anodal tDCS to left DLPFC each day for 10 days; 11 patients started fluoxetine (20mg/day) and continued for the duration of the study; and 10 patients received sham tDCS. At the end of 6 weeks, they found that both fluoxetine and tDCS led to significant improvements in BDI scores compared to the control. However, improvements occurred more rapidly with tDCS (See Figure 3).

**Figure 3: Average BDI Scores:** Shown are the averaged BDI scores for each group (active tDCS vs. Sham tDCS vs. FLU treatment) before (T0), 2 weeks after (T1), 4 weeks after (T2), and 6 weeks after (T3) onset of treatment. Lower BDI scores indicate an improvement. Figure taken from Rigonatti et al., 2008.
In 2008 Ferrucci and colleagues investigated the use of tDCS to treat 14 patients with severe drug-resistant MDD. All patients maintained their regimen of antidepressant medication and none received sham stimulation. The open design of their study, due to the lack of a control group, takes away some of the robustness of their findings; however, this decision was morally obligatory due to the severity of depression in these patients. Each patient received twice daily stimulation, separated by at least 4 hours, for 5 consecutive days. Stimulation lasted for 20 minutes at an intensity of 2mA with the anodal electrode placed over left DLPFC and the cathodal electrode over right DLPFC. Patients were assessed before, immediately after, and 4 weeks after treatment using HDRS, BDI, and a visual analogue scale [VAS] where patients would indicate their happiness by marking on a scale. They found that bilateral tDCS treatment of the DLPFC produced significant score improvements in both HDRS and BDI that lasted up to one month. More specifically, they observed substantial score improvements in 6 patients, moderate improvements in 6 patients, and no improvement in 2 patients one month after treatment.

In 2011 Brunoni and colleagues studied the effects of tDCS on 31 hospitalized patients with either MDD or bipolar depressive disorder. They followed the same protocol used by Ferrucci and colleagues in 2008; they applied tDCS bilaterally to DLPFC twice daily for 5 consecutive days and assessed patients using HDRS and BDI before, immediately after, 1 week after, and 1 month after treatment. They also chose an open study design, deciding not to use a control group. They confirmed that bilateral stimulation of DLPFC, stimulating the left with anodal current and the right with cathodal
current, improves mood in patients with MDD for up to 1 month. They also found that patients with bipolar disorder demonstrated an even greater improvement in HDRS and BDI scores than patients with MDD. Despite the outcome, the lack of blinding in their study creates doubt regarding the authenticity of their results, although it is strengthened by the findings of previous studies (Brunoni et al., 2011).

Several studies have shown no significant improvement in mood after stimulation of DLPFC using similar protocols to studies discussed previously. Despite following the same protocol used in a previous study (Fregni et al., 2006a), a 2009 study by Loo and colleagues found no significant changes after 5 sessions of anodal tDCS of DLPFC in patients with mild to moderate MDD. They did find significant improvement after 10 sessions. A 2012 investigation by Palm and colleagues failed to observe any significant improvement between sham and active tDCS conditions. Their cross-over double-blind study design consisted of 10 sessions of active tDCS and 10 sessions of sham tDCS over a 4 week period. Subjects (20 patients with MDD and 2 patients with bipolar disorder) were divided evenly into two groups, sham-active or active-sham, depending on the order of stimulation protocol they were to receive. Each session lasted 20 minutes at an intensity of 1 to 2mA with the anodal electrode placed over the left DLFPC and the cathodal electrode over the right supraorbital area. Using the 24 question version of the HDRS to assess improvement after each week, they found no significant difference between sham and active tDCS. Carry-over effects due to the cross-over design of this study and the use of antidepressants medications by patients may be to blame for the lack of significance observed (Palm et al., 2012).
In their 2012 study, Loo and colleagues evaluated 64 patients diagnosed with MDD following active or sham tDCS over a 6 week period. Subjects in the active group received 20 minutes of 2mA anodal tDCS every weekday for 3 weeks (total of 15 sessions). Electrodes were placed over the left DLPFC (anodal) and contralateral orbit (cathodal). After the first 3 weeks all subjects (regardless of grouping) were given the option to receive active tDCS treatment for another 3 weeks in an open phase of the study. All subjects were assessed using the Montgomery–Asberg Depression Rating Scale [MADRS] before starting treatment, after the 8th, 15th, 23rd and 30th session, and 1 week and 1 month after the cessation of treatment. The study revealed a significant improvement in MADRS score during the sham-controlled (blinded) phase, although results were “clinically modest” (Loo et al., 2012).

In summary, the use of tDCS as a treatment for depression may be as effective as pharmacological intervention with the added benefit of avoiding some of the less desirable side-effects. While some recent studies observed results that contradicted with previous positive findings (Loo et al., 2009; Palm et al., 2012), it seems plausible that the results of these investigations are attributable to insufficient treatment duration or carry-over effects due to study design. While stimulation over DLPFC proves to be effective, it would be interesting to see how tDCS stimulation over other areas (e.g. DMPFC) compares.
CONCLUSION

GENERAL PROPERTIES OF TDCS

Transcranial direct current stimulation is effective at modulating neural activity. The ability to increase or decrease activity depends on the polarity (direction) of current flow in relation to the orientation of the stimulated neuronal networks. This is demonstrated by increases in cortical activity during surface positive anodal stimulation that becomes inhibitory when the stimulating source is placed within the cortex. In theory an ideal current-to-neural axonal axis exists to optimally stimulate specific neuronal networks and may vary between individuals (Wagner et al., 2007, Wagner et al., 2009).

The duration of tDCS is also important. In general, as the duration of stimulation increases so does the duration of aftereffects. However, it has been shown that longer stimulation durations and the interval between multiple stimulation sessions can drastically alter the neuronal activity observed following tDCS. Difficulty understanding the differences in neuronal activity observed by changing the dosage (timing) of tDCS is largely due to the general lack of information regarding the mechanisms of plasticity.

The modification of neuronal activity produced by tDCS suggests that changes in plasticity, the strengthening or weakening of synaptic connectivity, is taking place. Past studies have shown that individual neuronal plasticity is regulated by both homeostatic and associative mechanisms (Markram et al., 1997, Stefan et al., 2000). This is demonstrated in neuronal networks by diminished excitability following simultaneous application of excitability enhancing PAS and anodal tDCS, and increased excitability
following simultaneous PAS and cathodal tDCS (Nitsche et al., 2007). It appears tDCS affects neuronal plasticity via homeostatic mechanisms by changing the overall amount of activity in the neuronal network. Thus, the contemporaneous increase or decrease in background activity induced by tDCS with the associative plasticity changes induced by PAS is most likely responsible for observed changes in neuronal activity. The relationship between plasticity and tDCS is further complicated by the reversal of neuronal activity observed when the interval between multiple tDCS sessions is increased or decreased. Regardless, the timing and level of activation of individual neurons is clearly related with the timing and activation of their associated neuronal network. The importance of the temporal relationship between homeostatic and associative plasticity may be the key in determining how changes in timing effect

**AS A TREATMENT TECHNIQUE**

Initial studies prove that tDCS is an effective treatment technique for many neurological diseases and disorders although its true potential is not yet realized. One recurrent theme is the lack of physiological evidence to support functional improvements, which is part of a larger lack of understanding regarding the mechanism of tDCS and how it affects neural networks and cellular processes and properties. While functional improvements are indicative of efficacy and changes in neural activity, without understanding how neurons respond to stimulation it is difficult to determine the best course of action for future studies.
For instance, the use of tDCS to treat motor deficits in stroke is very promising, but still far from understood. The basic concept is to increase activity in the lesioned hemisphere while decreasing activity in contralesional hemisphere. With the exception of a few studies, only a small amount of physiological evidence is available to support functional results, which in some cases did not completely correlated with the duration of aftereffects (Zimerman et al., 2010). Similarly, in tDCS studies of Parkinson’s disease, only one study showed that physiological changes (increased MEP amplitude) positively correlated with functional motor improvements following anodal stimulation of motor cortex (Fregni et al., 2006b). This suggests that stimulation of motor cortex compensates for the attenuation of thalamocortical activity caused by PD. The lack of physiological evidence from tDCS studies of other neurological diseases and disorders does not allow for observations like this to be made, leaving any physiological hypotheses unreliable and unsupported. For example, studies involving the use of tDCS in Alzheimer’s disease and depression leave no direct evidence to support any hypothesis regarding the physiological changes that may result from stimulation. While functional improvements are seen in visual recognition tasks (AD) and changes in mood (depression) without direct evidence it is not possible to objectively compare the functional improvements observed to other findings with any real certainty. This leaves suspicion that functional improvements may be the result of other factors and not directly attributable to tDCS.

Another recurrent theme is a lack of prolonged duration of tDCS treatment (not to be confused with the duration of an individual tDCS session). Thus far, the longest duration of tDCS treatment observed for any neurological disease or disorder was never
longer than a few weeks (in the studies reviewed by this thesis). Despite short treatment durations, aftereffects often persisted from several hours to several weeks.

The lack of monitoring of certain variables and factors is also potentially problematic. While many studies did analyze the statistical influence of some variables, such as gender, mental state, disease state, and age; other variables like temperature, heart rate, blood pressure and blood-glucose often go unreported. While it is unlikely that these variables will significantly impact comparisons of neurological activity, changes in routine and behavior by participating in tDCS studies, as well as differences in physiology between individuals, may influence neuronal behavior and response to tDCS.

Electrode placement is also a major factor when treating neurological diseases and disorders. In computational modeling studies, electrode placement has been shown to greatly influence current densities (Wagner et al., 2007), which is supported by physiological findings (Nitsche & Paulus, 2000). This emphasizes the importance of electrode placement for investigators, not only to stimulate the appropriate cortical areas, but also to obtain significant current densities to influence neuronal behavior.

Finally, there are currently no studies that investigate the use of tDCS as a preventative measure against certain neurological diseases and disorders. Since many neurological diseases are preceded by dysfunction of specific cortical areas it seems possible that tDCS may be able to help prevent further progression of the disease. This might include halting the development of Lewy bodies and Lewy neurites in Parkinson’s disease or amyloid plaques and neurofibrillary tangles in Alzheimer’s disease by
activating autophagy pathways, or preventing the neurotoxic effects of prolonged exposure to glucocorticoids via stress pathways (i.e. HPA axis) in major depression by inhibiting over-activation. Along the same lines, current tDCS stroke studies have been limited to treating patients with chronic stroke, while other treatment options are relied upon for acute and subacute stroke. It appears plausible that tDCS may be beneficial as an earlier treatment to help combat PIDs and modulate neuronal activity to help prevent apoptosis.
REFERENCES


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