MODULATORY EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON TRIMODAL INTEGRATION

Author

IZZAT FATIMA

NUST2015-MS-BMS-00000117377

Supervisor

Dr. Muhammad Nabeel Anwar

Co-Supervisor

Muhammad Samran Navid

Department of Biomedical Sciences and Engineering

School of Mechanical and Manufacturing Engineering

National University of Sciences and Technology

H-12 Islamabad, Pakistan

April 2018

MODULATORY EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON TRIMODAL INTEGRATION

Author

Izzat Fatima

Registration Number

NUST2015-MS-BMS-00000117377

A thesis submitted in partial fulfilment of the requirements of the degree of Masters of Science

In

Biomedical Sciences

Thesis Supervisor

Dr. Muhammad Nabeel Anwar

Department of Biomedical Sciences and Engineering School of Mechanical and Manufacturing Engineering National University of Sciences and Technology H-12 Islamabad, Pakistan

Thesis Acceptance Certificate

It is certified that the final copy of MS Thesis written by **Izzat Fatima** (Registration No. **NUST2015-MS-BMS-00000117377**), of SMME (School of Mechanical & Manufacturing Engineering) has been vetted by undersigned, found complete in all respects as per NUST statutes / regulations, is free of plagiarism, errors and mistakes and is accepted as partial fulfilment for award of MS/MPhil Degree. It is further certified that necessary amendments as pointed out by GEC members of the scholar have also been incorporated in this dissertation.

Signature:_____

Name of Supervisor: Dr. Muhammad Nabeel Anwar

Date:_____

Signature (HOD):_____

Date:_____

Signature (Principal):_____

Date:_____

Declaration

I, Izzat Fatima, certify that this research work titled "**Modulatory effect of Transcranial Direct Current Stimulation on Trimodal Integration**" is my own work. The work has not been presented elsewhere for assessment. The material that has been used from other sources has been properly acknowledged / referred.

_____

Izzat Fatima

NUST-2015-MS-BMS 00000117377

Plagiarism Certificate

(Turnitin Report)

This thesis has been checked for Plagiarism. Turnitin report endorsed by the Supervisor is attached at the end of this report.

_____

Izzat Fatima

NUST-2015-MS-BMS-00000117377

Dr. Muhammad Nabeel Anwar

Signature: _____

Copyright Statement

- Copyright in text of this thesis rests with the student author. Copies (by any process) either in full, or of extracts, may be made only in accordance with instruction given by the author and lodged in the Library of NUST School of Mechanical & Manufacturing Engineering (SMME). Details may be obtained by the Librarian.
- This page must form part of any such copies made. Further copes (by any process) may not be made without the permission (in writing) of the author.
- The ownership of nay intellectual property rights which may be described in this thesis is vested in NUST School of Mechanical & Manufacturing Engineering, subject to any prior agreement to the contrary, and may not be made available for use by third parties without the written permission of the SMME, which will prescribe the terms and conditions of any such agreement.
- Further information on the conditions under which disclosures and exploitation may take place is available from the Library of NUST School of Mechanical & Manufacturing Engineering, Islamabad.

Acknowledgements

All the praise to the All Mighty Allah who's blessings were with me through all these years. Foremost, I would like to be grateful to my parents Mr. and Mrs. Muhammad Iqbal for their continued prayers, love and unconditional support, both emotionally and financially during my MS degree. The understanding shown by them during all these years is greatly appreciated. I would also like to thank my beloved siblings, Nudrat, Hurmat and Mahrukh and M. Fouz for motivating, supporting and encouraging me in achieving my goals.

I would like to express my genuine gratitude to my supervisor Dr. M. Nabeel Anwar for the ceaseless support during my MS final year research work, for providing a platform full of research opportunities in NUST, for his enthusiasm, immense knowledge patience, motivation, and invaluable suggestions. His supervision helped me in all the time of research as well as in writing of my thesis. I could not have anticipated having a best advisor and a counselor for my research. I also express my sincere gratefulness to M. Samran Navid, my co-supervisor for providing his valuable time, support, extensive guidance and skillful technical assistance.

I would also like to show my utmost regard to my best friends, Amna Malik, Muadh Solaija and Usman for their support and care that helped me overcome setbacks and stays focused on my research project. Thanks for the friendship and memories and for their cheerful company and consistent help during all these years.

Lastly, I am grateful to HSL members, those you have volunteered in my research experiments those with whom I have had the pleasure to work during this project. I would like to thank Dr. Abdul Ghafoor (Principal, SMME), my teachers and thesis committee members; Dr. Adeeb Shehzad, Dr. Umar Ansari, and Dr. Syed Omer Gillani for their guidance and support.Lastly, I would also like to thank all administration and the staff of SMME for their technical support.

Izzat Fatima

I have dedicated my thesis to my parents and my siblings for their immense love, support and motivation.

Abstract

Transcranial direct current stimulation is a neuromodulatory and noninvasive brain stimulation procedure with the purpose of inducing polarity specific alteration in human brain, resulting in either increase or decrease in brain excitability. Human tDCS studies have focused on bimodal sensory integration such as audio-visual, visuo-tactile, visual-motor integration but to date, there is no study investigating the modulation of visual, auditory and tactile processing. The objective of this study is to explore whether bihemispheric brain stimulation (dual tDCS) could be effective in modulation of perception of human in the incidence of auditory, visual and tactile stimulation in a numerosity judgment task. Human brain generally processes signals from multisensory modalities at any split second and is consequently posed to two different dilemmas: which area of the brain is important in merging these signals and which of the signals are caused by an ordinary thing. Posterior Parietal Cortex is the hub of multisensory information that is the information from different modalities actually converges here. We aimed to explore the role of posterior parietal cortex (PPC) on trimodal integration and Bipolar Bihemispheric tDCS was employed for altering the brain function. For this, 25 healthy participants performed the task and were randomly allocated for the 3 groups (n=3), Sham tDCS (Stimulation 1), Active Anodal tDCS (Stimulation 2) and Active Cathodal tDCS (Stimulation 3). All participants participated in all session which consists of a baseline session and a tDCS session with a gap of one week for a total of three weeks, while receiving cathodal, anodal and sham tDCS (2mA, 20min) to bilateral posterior parietal cortices. The results reveal that down- or up- regulating the cortical excitability by tDCS can reduce or facilitate audiovisual and tactile interactions respectively i.e. right PPC is involved in the integration of trimodal sensory information and reversal of such effects was induced by left PPC.

Keywords: neuromodulation, posterior parietal cortex, dual tDCS, triomodal integration, anodal tDCS, cathodal tDCS, sham tDCS

Table of Contents

List of Figures

List of Tables

List of Acronyms

AMPA	α-Amino-3-hydroxy-5methyl-4-isoxazole propionic acid
$ANOVA_{RM}$	Repeated measure anova
BS	Brief stimulation
cAMP	cyclic adenosine monophosphate
CREB	cAMP response element binding protein
Db	Decibel
EEG	Electroencephalography
ERP	Event related potentials
FDA	Food and drug administration
fMRI	Functional magnetic resonance imaging
GABA	Gamma-Aminobutyric acid
Hz	Hertz
KHz	kilohertz
lPPC	Left posterior parietal cortex
M1	Pimary motor cortex
mA	milliAmperes
MEG	Magnetoencephalography
Ms	milliseconds
NMDA	N-Methyl-D-Aspartic acid
PPC	Posterior parietal cortex
RD	Ramp down
rPPC	Right posterior parietal cortex
RU	Ramp up
S1	Primary somatosensory cortex
tACS	Trans cranial alternating current
tDCS	Trans cranial direct current stimulation

tPCS	Trans cranial pulsed current
tRNS	Trans cranial random noise
V1	Primary visual cortex

1 INTRODUCTION

1.1 Transcranial Electric Current Stimulation

Transcranial electric current stimulation is one of the brain stimulation techniques, which can improve performance of cognitive functions in humans and recover the clinical condition of different kinds of patients like aphasia, language processing, stroke, motor and cognitive deficits (Andre Russowsky Brunoni et al., 2012; Monti et al., 2013; Ruffini & Barcelona, 2013). It emerges that humans can significantly gain from the easy-to-apply and affordable procedure (Riggall et al., 2015). The tES affects the neuronal states via the application of current waveforms transcranially. The forms of tES includesTranscranial pulsed current stimulation, Transcranial direct current stimulation, Transcranial random noise stimulation, and Transcranial alternating current stimulation. These forms of current are considered well-tolerated and operate by inducing changes in the electric activity both outside and inside the neurons, altering the resting membrane potential and the as a result, modifying neuronal synaptic efficiency (Goetz & Peterchev, 2012; Liebetanz, 2002; Paulus, 2003a). These alterations are not sufficient to stimulate action potentials but can produce disparity in the response threshold of neurons being stimulated (Fertonani & Miniussi, 2017). The tES involves the administration of weak intensity current (1-2mA) by a stimulator, driven by a battery, between the two electrodes (cathode and anode), positioned on the targeted area of the brain. The electrodes are generally of square shape, conductive and large inserts of sponges are enclosed in it (saline-soaked, 20-35cm^2). The current reaches the targeted cortical area where the electrode is attached and the extra cortical layers to arrive at the cortex, thus modulating the membrane polarity of the targeted neurons with an area underlying neural tissue (Siciliano, Hirata, & Kelly, 2016).

1.2 Models of tES

There are four models, out of which three models of tES link the effects of tES at the level of neuron to the effects at the level of human behavior. Mostly, with anodal tDCS stimulation, the potential of neuronal membrane is depolarized, thus a human behavioral improvement will be obtained. Conversely, with cathodal tDCS stimulation, the neuronal membrane potential is hyperpolarized, resulting in worsening of behaviour (Chrysikou et al., 2016; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Michael A. Nitsche et al., 2003; van Dun, Bodranghien, Mariën, & Manto, 2016a). In addition to this, the tES models also predict

behavioral outcome which alters the modulatory effects that are stimulated by tES and it ignores overall transitional levels that integrate plus mediate these effect.

1.2.1 Activity-Dependent Model

This activity-dependent model includes a certain rank of complexity and the stimulation effect is dependent upon the action of the system. Hence, this model deals with the activity level of neurons being stimulated, resulting in increase or decrease in excitability as shown in figure 1.1 (Chrysikou et al., 2016; Fertonani & Miniussi, 2017; Krause & Cohen Kadosh, 2013).

1.2.2 Network Activity-Dependent Model

In this kind of approach, the effects induced by tES are responsive to the particular state of networks. Therefore, the stimulation effects are dependent upon the level of activity of the stimulated networks this level of network activity may possibly has the potential to change the network state for better performance or worsening of it in one or more functions which are normally performed by the neuronal network as illustrated in figure 1.1 (Chrysikou et al., 2016; Fertonani & Miniussi, 2017; Krause & Cohen Kadosh, 2013).

1.2.3 Excitation-Inhibition Balance Model

This model integrates the vital knowledge from neuropsychiatry and neuroscience and stimulation results to discover the major factor for the maintenance of functions related to brain and maintain the equilibrium between inhibitory and excitatory inputs in the brain. The tES data concluded MEG (magnetoencephalography) revealed so as to alter the concentration of excitatory (glutamate) and inhibitory (GABA) neurotransmitters in tDCS stimulation. Hence, neurostimulation (Stagg & Nitsche, 2011) can assist examinations of brain networks and distinguishing the outcomes of tES and its types on these brain networks. Similar technique has been tested for different types of tES specifically tDCS and neuro-imaging techniques to access the cortical associations and their underlying relations (Fertonani & Miniussi, 2017; Krause & Cohen Kadosh, 2013).

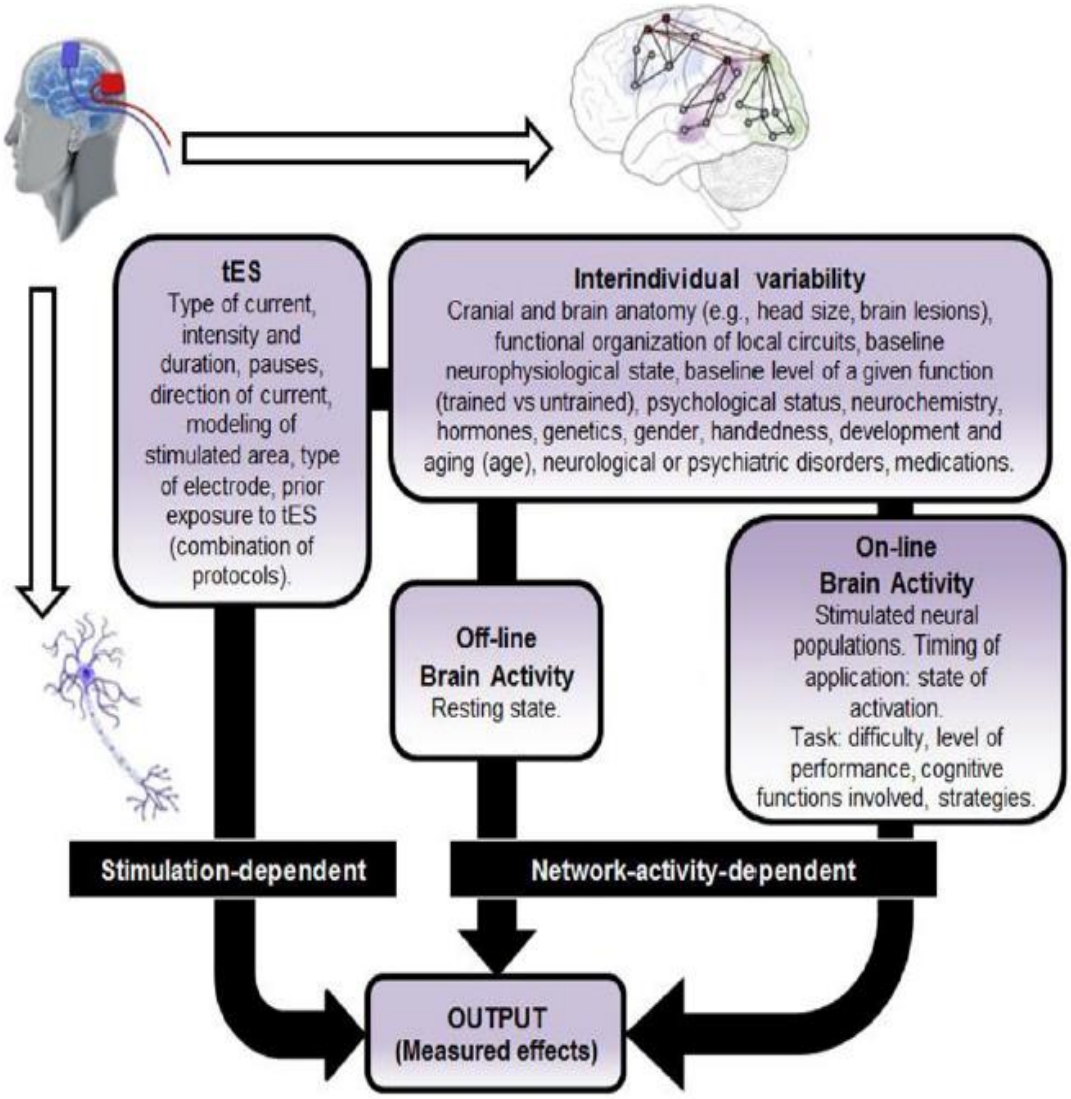


Figure 1.1- ***Factors affecting tES models****. In activity dependent model, the effects of tES procedure in excitability termsis dependent upon the relation of numerous elements related not only to the stimulation, but the participants under study. Whereas, in stimulation-dependent model, the measure of the effect of tES may be completely described, by taking into account the tES effects at the level of neuron. The inter-individual variability depends upon quite a lot of factors like psychological status, age and gender etc, which can influence cortical excitability* (Fertonani & Miniussi, 2017; Li, Uehara, &*Hanakawa*, 2015)

1.3 Transcranial Direct Current Stimulation

tDCS (Transcranial direct current stimulation) has become an important research and rehabilitation means for investigating neuropsychological processes crucial for human cognition and behaviour (Ruffini & Barcelona, 2013). tDCS is a neuromodulatory, non-invasive, portable and an affordable technique which is used to influence the brain activity and its associated alterations in brain behaviour relationship (Fertonani & Miniussi, 2017; Michael A. Nitsche et al., 2008; Paulus, 2003a; Ruffini & Barcelona, 2013; van Dun et al., 2016a). Neurostimulation helps in modulating the brain regions by exciting or inhibiting , thus monitoring the consequences on behavioral effect. Therefore, tDCS is increasingly applied for healthy subjects and for the patients in order to deduce about the connection between the targeted regions of the brain and its behavior (Ruffini & Barcelona, 2013).

1.4 Basic Working Principle

tDCS is a Transcranial electrical current stimulation techniques which involves the application of weak and a low intensity current (0.5-2mA) (Woods et al., 2016) on the targeted regions of brain through two or more electrodes placed on the scalp. The current partially penetrates the cranium and goes into the brain. The current flows from an active to a reference electrode, resulting in the cortical excitability or inhibition.

1.5 Mechanism of action of tDCS

Two mechanisms appear to cause tDCS effects, Anodal and Cathodal tDCS stimulation and the core findings may possibly be summed up as follows:

1. tDCS effects, in the initial stage, might be enlightened by modulation of inactive membrane potentials of the region of brain being stimulated. The way the stimulation alters the brain function is either by causing the neuron's resting membrane potential to hyper polarize or depolarize (Figure 1.2).
2. tDCS effects, in the later stages, might be due to "long-term potentiation (LTP)" like and "long term depression (LTD)" like plasticity mechanisms.

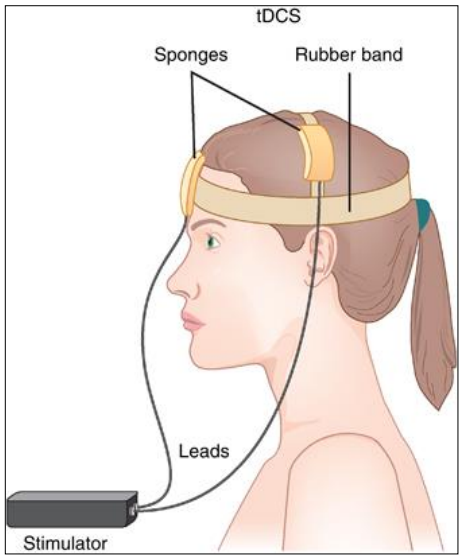


Figure 1.2- ***tDCS stimulation setup****. A battery-driven device delivers a constant current of up to 2 milliAmperes the two electrodes (positively charged anode and negatively charged cathode) can provide different kind of stimulation depending upon the targeted brain region*(Andre R Brunoni, Boggio, Ferrucci, Priori, & Fregni, 2013).

1.5.1 Anodal tDCS

Anodal tDCS is suggested to induce LTP as a result of enhanced firing rate i.e., influx of sodium ions (Na^{+}) occur and it affect the resting membrane potential in such a way to compose it more positive, making the cell more expected to be fired (Figure1.3). Post synaptic depolarization induced by anodal tDCS, caused by changed pre-synaptic input because of the changed firing rates which results in an increased NMDA ('N-Methyl D-Aspartate') and AMPA ('α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid') receptor efficiency resulting in an increase of the intracellular Ca^{+2} level (Mohammadi, 2016; Paulus, 2003a; Woods et al., 2016).

1.5.2 Cathodal tDCS

Cathodal tDCS is suggested to induce long-term depression (LTD) most of the time by reducing the firing rate i.e., efflux of potassium ions (K^{+}) occur and it causes the resting membrane potential to become more negative , making the cell less likely to fire (Figure 1.3). Post synaptic depolarization induced by cathodal tDCS, caused by changed pre-synaptic input because of the changed firing rates which results in an increased GABA (gammaaminobutyric acid) receptor efficiency concluding in a decrease of the intracellular Ca^{+2} level (Bear & Malenka, 1994; Kronberg et al., 2017; Paulus, 2003b).

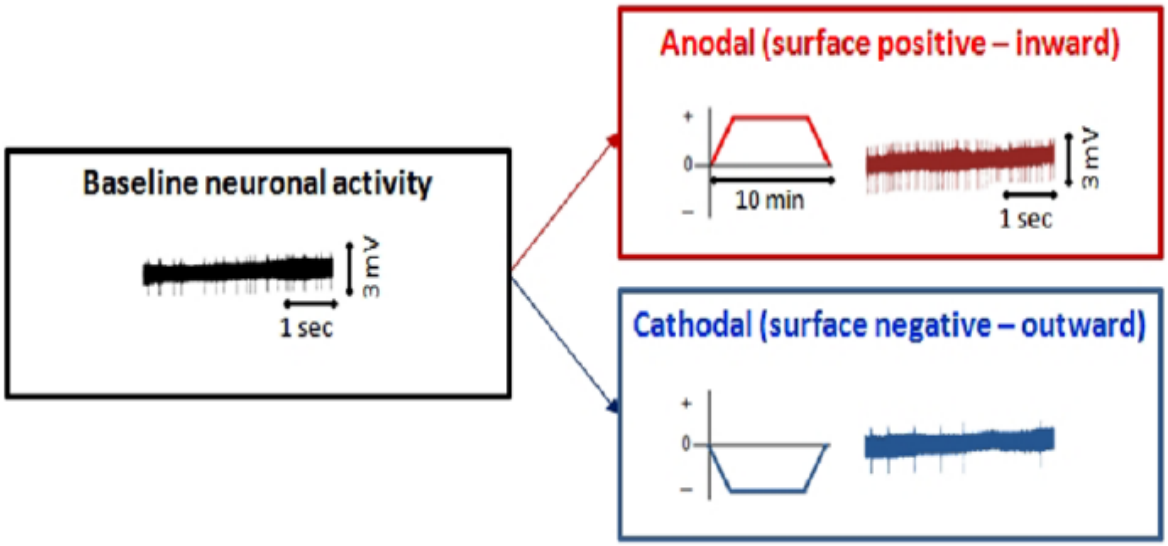


Figure 1.3- ***Comparison of neuronal activity between baseline and active tDCS stimulation.****The Figure illustrates how a transcranial direct current polarization (positively charged anode and negatively charged anode) alters the spontaneous firing activity of neurons in a targeted area of the brain. The figure on the left shows a baseline activity of neurons. The upper right figure(red) shows the positive polarization i.e. increase in the firing rate of the neurons, whereaslower right figure(blue) shows the negative polarization, indicating a decline in activity or no activity* (Fertonani &*Miniussi*, 2017).

.

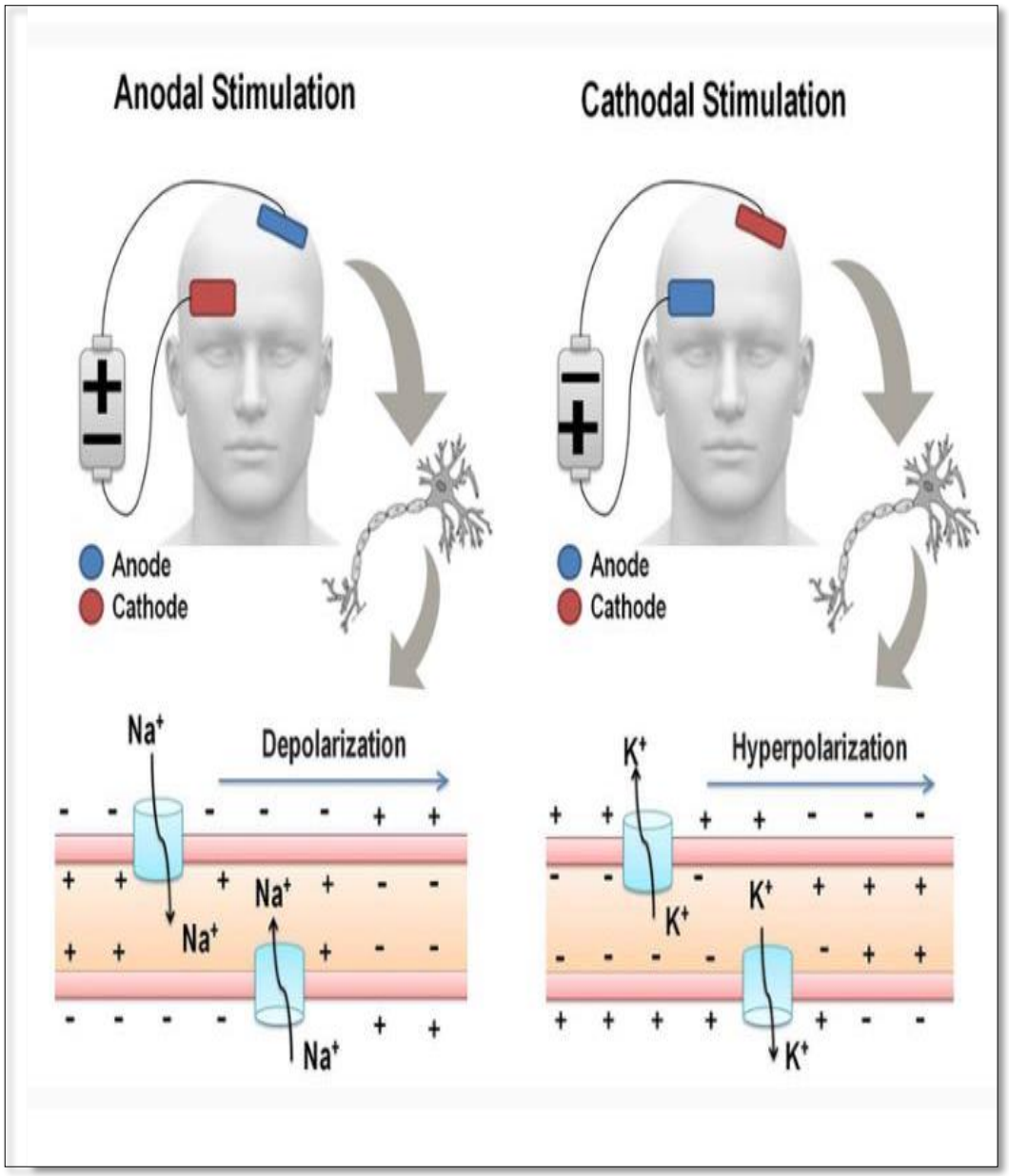


Figure 1.4- ***Effect of Anodal and Cathodal stimulation on membrane polarization****. Cathodal stimulation hyperpolarizes (efflux of K ions occur) the neuronal membrane (blue) and anodal stimulation depolarizes (influx of Na ions occur) the membrane (red)(Cabral et al., 2015) .*

1.5.3 Neurological mechanism of tDCS

Anodal stimulation is the type of stimulation which depolarizes the neuronal membrane and the glutamate, which is the primary excitatory neurotransmitter at almost every single synapse in the nervous system, and is released by pre-synaptic neuron and binds with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-Methyl D-Aspartate) receptors (Stagg & Nitsche, 2011) (Figure 1.4). Even though

depolarization is occurring , there is an increase of intracellular Ca^{+2} in the post synaptic neuron, which results in activation of protein kinases, such as Calcium/calmodulin dependent kinase (CaMK). In turn, protein kinases modulate several neuronal signaling pathways leading to transcription, translation as well as insertion of new glutamate receptors. In long term potentiation, CaMK trigger), a transcription factor, cAMP response element binding protein (CREB) which mediates gene transcription and formation of new proteins as illustrated in figure 1.5and 1.6.

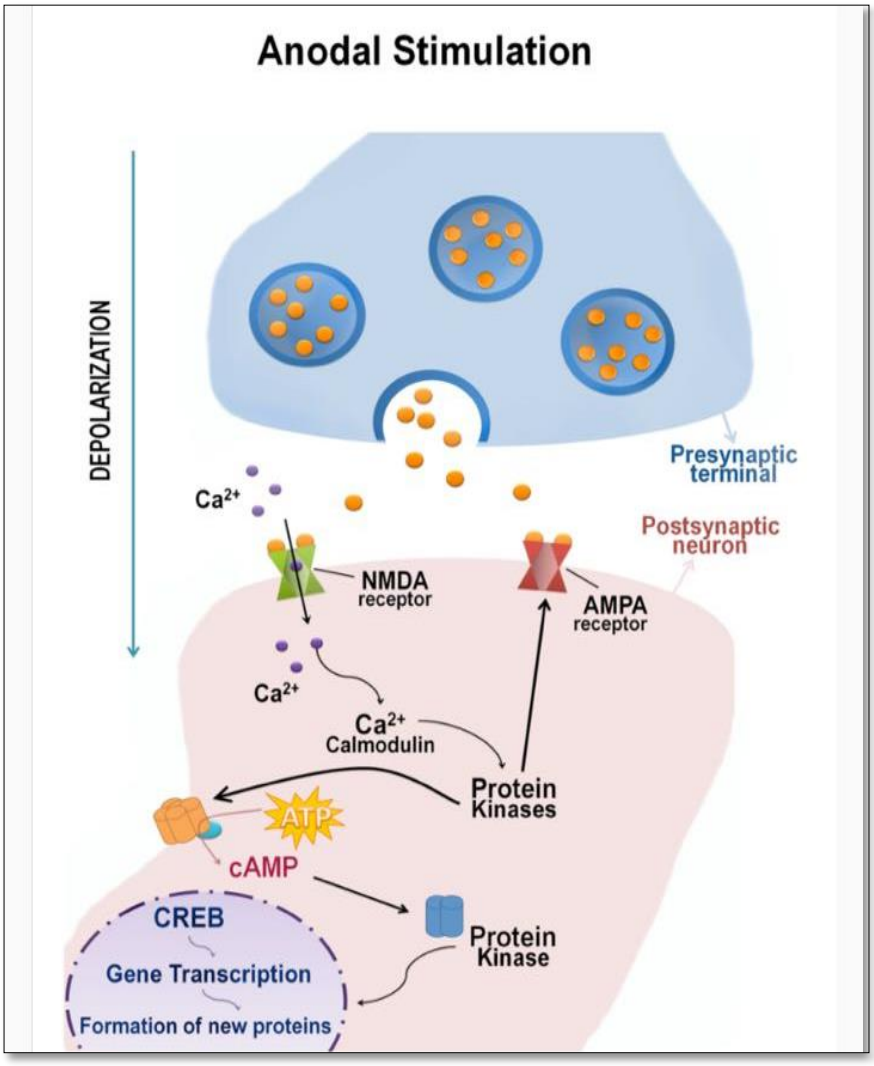


Figure 1.5- ***Mechanism of LTP induced by tDCS by anode electrode and the outcomes of excitatory stimulation on the synapses of superficial neurons in the target cortical region.*** *The glutamate is released from pre-synaptic membrane and binds to post-synaptic membrane i.e. NMDA and AMPA receptors. There is an increase in the calcium levels, which results in the activation of protein kinases. In long term potentiation CaMK activate CREB (cAMP response element binding protein) which is a transcription factor, which mediates gene transcription and formation of new proteins(Cabral et al., 2015).*

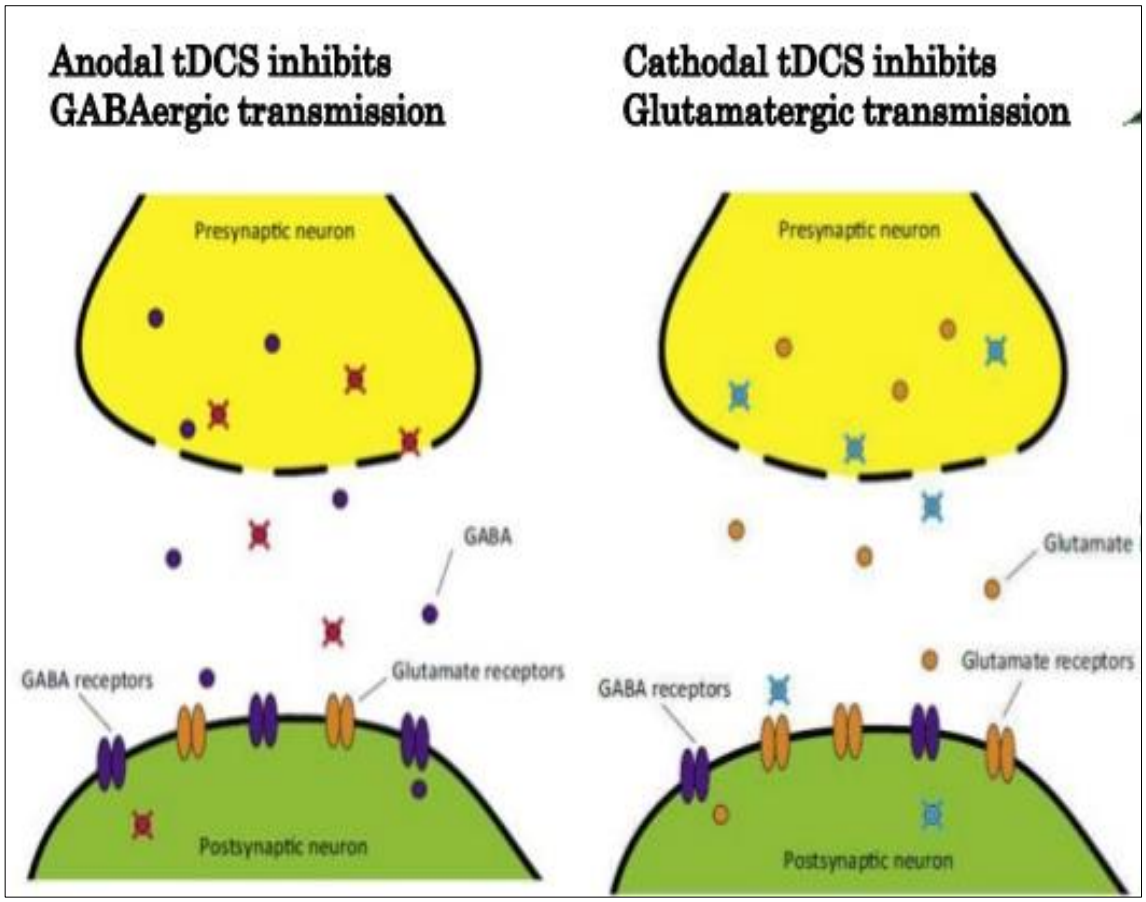


Figure 1.6- ***The mechanism of action at the synaptic level****. Neurobiological effects of tDCS indicates that the anodal tDCS inhibits GABAergic receptors and cathodal tDCS inhibits Glutamatergic receptors*(Filmer, Dux, & Mattingley, 2014)

1.6 Parameters of tDCS Stimulation

tDCS stimulation is dependent upon the type of stimulation parameters and various factors that need to be defined. These factors are inclusive of size and positioning of electrode, intensity, duration of stimulation, quantity of sessions and interval between the sessions. Different amount of electric current can be delivered just by varying these parameters, thus inducing diverse psychological effects (M. Nitsche, Antal, Liebetanz, & Lang, 2007). These parameters are discussed in detail in session from 1.61-1.68.

1.6.1 Current intensity

The total current intensity applied on the scalp through electrodes, ranges from 0.5-2mA. This can reach broad cortical areas under and between electrode surfaces. Up to 2 mA current can be applied for 20minutes with minimal pain or burning sensation and no skin damage (Mulkey, Herron, & Malenka, 1993). The current being injected, flows from anode to cathode as shown in the figure 1.7 and 1.8.

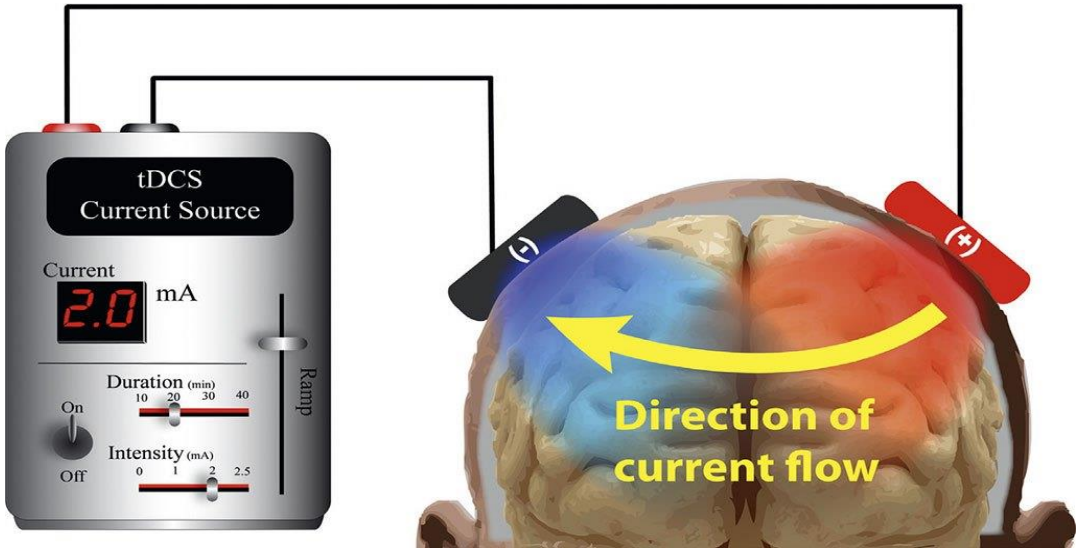


*Figure 1.7- **Direction of current flow in tDCS.** Current flows from Anode (red electrode) to Cathode (blue electrode) (Fertonani & Miniussi, 2017).*

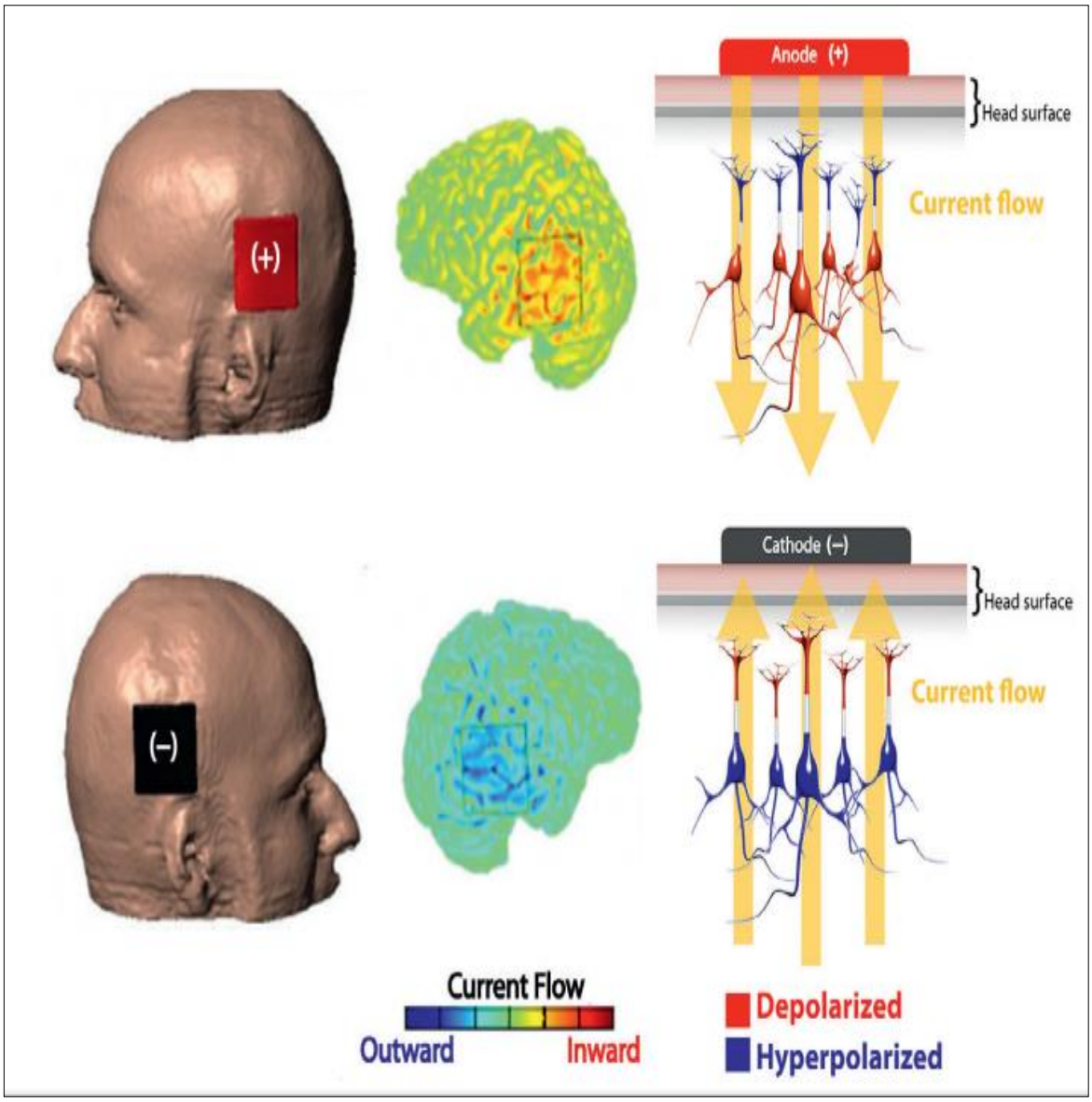


Figure 1.8- ***Polarity of electrode with tDCS determines the direction of flow of current.*** *Brain polarization influences the regions of the brain (sub-cortical and cortical regions) being stimulated. (+) in figure demonstrates the current flow through positive electrode in tDCS. The current surpasses via scalp and bone, prior toentering the sub-cortical and cortical areas of the brain. Under the anode, somatic regions become depolarized (red) whereas the apical dendritic areas of neurons become hyperpolarized (blue). (-) in figure explains the direction of current through cathode. The current leave behindthrough the scalp and the bone, prior to reaching sub-cortical and cortical areas of the brain. Under the cathode where the pyramidal cortical neurons are present, somatic regions turn out to be hyperpolarized and the apical dendritic areas of neurons happen to be depolarized.*

1.6.2 Current density

The current density of tDCS electrodes is determined by the electrodes' surface area and the intensity being used. Square electrodes measuring 5x5 are typically used for stimulating various regions of the brain(Andre R Brunoni et al., 2013; Michael A. Nitsche et al., 2005). The larger the size of active electrode, the larger area will be needed for stimulated and the density of current will be small. (Poreisz, Boros, Antal, & Paulus, 2007). The current densities up to 25mA/cm^2 donot induce brain tissue damage or painful sensation (Paulus, 2003b; Poreisz et al., 2007).The density of the current is measured by the following formula;

$$\boldsymbol{Current\ Density = Total\ Current / Total\ Area}$$

The following table 1.1 shows the current densities keeping the total current 2mA.

*Table 1.1- **Current density with respect to electrode's surface and size**. The current densities delivered to the humans can vary from 0.028-0.080mA/cm^2. The following table is according to 2mA current.*

Electrode size (cm)	**Electrode surface (cm^2)**	**Current density (mA/cm^2)**
5x5	25	0.080
5x7	35	0.057
7x10	70	0.028

1.6.3 tDCS Electrodes

The purpose of electrodes is to facilitate the delivery of current from the stimulation device to the region of brain without any skin injury (Andre Russowsky Brunoni et al., 2011). The assembly of tDCS' electrodes generally consists of metal or conductive rubber electrodes, sponge inserts for the electrode, an electrolyte (gel, conductive cream or saline solution) based contact medium to ensure efficient delivery of current to the scalp (M. Bikson, Datta, Rahman, & Scaturro, 2010; Marom Bikson et al., n.d.; Andre R Brunoni et al., 2013; Martin, Liu, Alonzo, Green, & Loo, 2014). Generally in the tDCS experiments, saline soaked sponges are used with elastic headbands which ensure electrodes' placement (Poreisz et al., 2007; Woods et al., 2016).

1.6.4 tDCS Montages

Depending on the amount of electrodes as well as affected hemispheres, 10-20 EEG system is employed to pinpoint the region on the skull. The conventional types of montages are as follows: double monopolar montage in which two electrodes are active, one is placed on the scalp and the reference electrode is placed outside the scalp .Bipolar montage is the intervention in which both reference and active electrodes are placed on scalp. Monoploar montage is the same as first type. The only difference is that only one electrode is placed on the scalp.

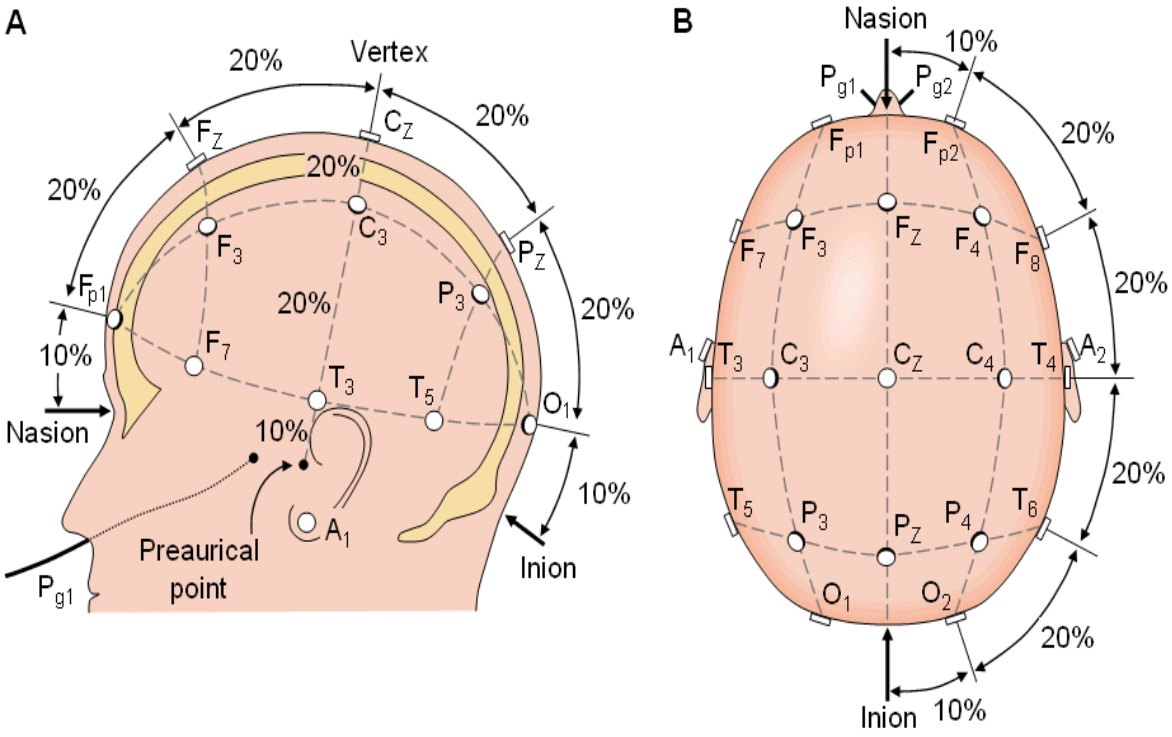


Figure 1.9- ***Figure represents 10-20 EEG system to localize brain areas.****(A) It implies four landmarks of head: the nasion is the point between the nose and forehead, the preaurcile point (right and left) the inion is the farthest spot of the cranium from the backside of the skull which is signified by a high up bump. Every point is denoted by a number and a letter. The letter O, C, P, T and F denote occipital, central, parietal, temporal and frontal respectively. (B) The odd numbers (1,3,5,7) indicates those present on the left hemisphere,while the even numbers (2,4,6,8) indicates the location of electrodes on the right hemisphere (Schestatsky, Morales-Quezada, & Fregni, 2013).*

Recently, for accurate placement of electrodes, four different groups of tDCS montages and 12 subgroups are made in order to avoid incorrect placement of electrodes. For describing the electrodes, the position of anode is described first. The groups are unilateral, bilateral, midline and dual channel. Whereas, the subgroups such as bipolar unilateral, monopolar unilateral, multiple monopolar unilateral, bilateral bipolar-dual channel non balanced, bilateral multiple monopolar, midline monopolar, midline bipolar balanced, midline bipolar-non balanced, midline double monopolar dual channeled and bilateral double monopolar dual channeled are illustrated in the figure 1.10. Each montage can be used to stimulate different neural networks (Nasseri, Nitsche, & Ekhtiari, 2015).

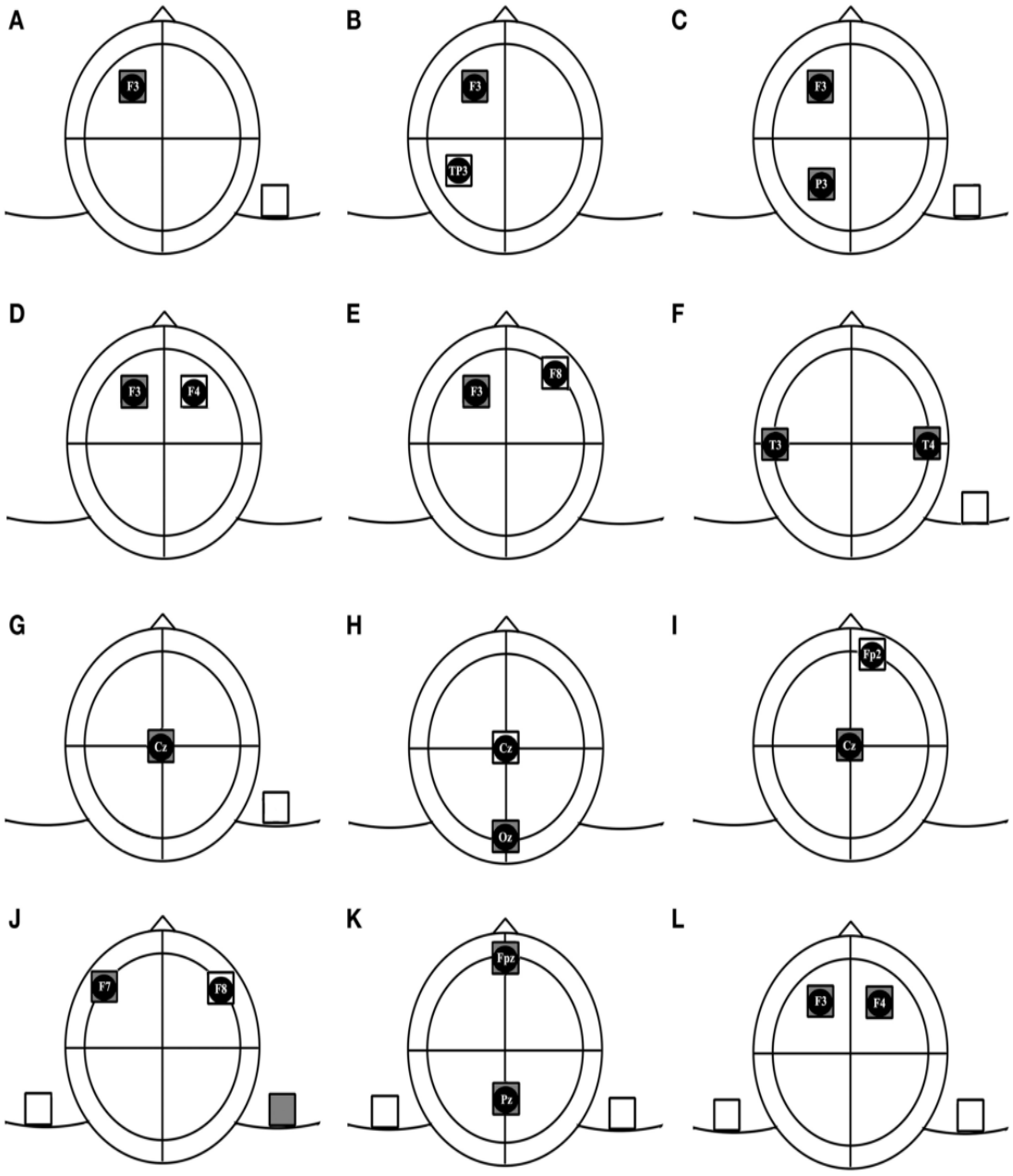


Figure 1.10- ***The subdivision of Transcranial direct current stimulation montages.*** *(1) monopolar unilateral montage, (2) bipolar unilateral montage, (3) multiple monopolar-unilateral montage , (4) bipolar-bilatleral non-balanced montage , (5) bipolar bilatleral non-balanced montage, (6) bilateral multiple monopolar montage, (7) midline monopolar montage, (8) midline bipolar balanced montage, (9) midline bipolar-non balanced montage, (10) dual channel bipolar montage, (11) midline double monopolar with dual channeled montage and (12) bilateral double monopolardual channeled montage (Nasseri et al., 2015).*

1.6.5 Sessions and Duration of tDCS

Multiple sessions have collective effect as compared to single session study and are employed for inducing long-lasting effects of the stimulation (Andre Russowsky Brunoni et al., 2012).The standard session of tDCS should last between 5-30 minutes and it has been suggested that five minutes is the minimum duration of stimulation required to cause a notable effect which can lasts beyond the conclusion of any experimental task. The studies which are based on multiple sessions with a stimulation of 2mA with 10-20 minutes duration, in order to avoid cross over effects from previous stimulation, the maximum gap to be given should be at least a week. The was-out effects of the previous stimulation are dependent upon both the current and the duration of stimulation (Grimaldi et al., 2016; Ruffini & Barcelona, 2013)

1.6.6 With-in and between Subjects Design

The design depends on the targeted population in the study. In multiple groups design, based on the intervention type selected (active anodal or cathodal and sham tDCS) the groups are defined and the interventions are randomly assigned. Unlike multiple groups, multiple sessions deal with only one group in which one intervention type is given for at least one session per subject. Each design has its own pros and cons, the major concern is carry over effects and habituation in multiple session. Whereas, large sample sizes is needed in single session study design.

1.6.7 Offline verses Online Conditions

tDCS intervention can be given in two diverse circumstances, offline and online. It greatly depends upon the type of effects which needs to be focused. When the effect of tDCS is to be monitored along with another intervention i.e., training sessions or physical/cognitive therapy or it is to be measured for the duration of stimulation (tDCS) , then the study applies an online approach. In contrast, if the experimental task is performed either pre-post procedure (performed before and after intervention) or post to the intervention, then the study is an offline approach (Filmer et al., 2014; Zhao et al., 2017). The combination of the online and offline designs is another possibility for an advance procedure design, where the effects of both the experimental task as well as the stimulation (Ruffini & Barcelona, 2013; Thair, Holloway, Newport, & Smith, 2017).

1.6.8 Sham Procedure

Sham tDCS acts as a control procedure which is administered in the same manner as of active sessions like anodal or cathodal tDCS, but the current is delivered for 1 min with a ramp up and ramp down time of 30s. To make sure that the consequences are the result of stimulation and not due to practice or a placebo effect, the information is frequently compared with the measuring before and after the active sessions and the sham session. This brief periods of stimulation doesn't alter cortical excitability (Dissanayaka, Zoghi, Farrell, Egan, & Jaberzadeh, 2018; Thair et al., 2017; van Dun, Bodranghien, Mariën, & Manto, 2016b).

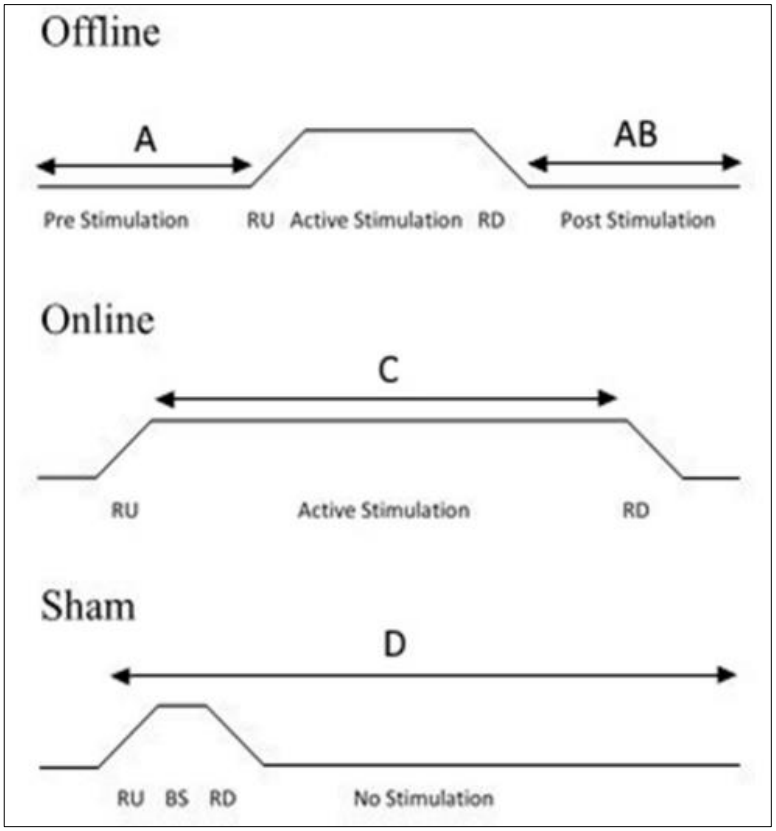


Figure 1.11- ***Diagram illustrating types of experimental protocol.*** *(A) Offline stimulation consists of a period of pre-stimulation in which a task is completed, followed by a stimulation period then a post-stimulation task. (B) Offline stimulation may consist of a post-stimulation task only. (C) Participants receive stimulation during task in an online stimulation. (D) Sham stimulation, the current ramps up (RU) followed by brief stimulation (BS) period then followed by a ramping down (RU) of the current. The current then remains off for the rest of the experimental task(Vaseghi, Zoghi, & Jaberzadeh, 2015).*

1.7 tDCS Safety and Side Effects

By employing the experimental protocols (28) and stypical current range the tDCS side effects are short lived and benign. Brunoni (29), in a recent systematic review, assembled data from various studies performed up to 2010, 63 percent (%) described one adverse effect whereas 56% revealed adverse effects out of 172 articles. Importantly, after systematic analysis, the pace of common adverse effects was comparable between sham and active studies. The effect includes itching (32.9% vs. 39.3%) respectively, headache 16.2 % vs. 14.8%, tingling 18.3% vs. 22.2% , discomfort 13.4% vs. 10.4 % and burning 10% vs. 8.7% . According to FDA, the severe adverse effects are those in which the upshot is hospitalization, disability or permanent damage to the brain, death, congenital anomaly or birth defect, required intervention to prevent permanent damage (for implantable device) and other serious events like seizures anaphylactic reactions , cardio respiratory arrest (M A Nitsche et al., 2004; Michael A. Nitsche et al., 2003; Tadini et al., 2011). In contemporary tDCS literature from 1998 till 2014, more than 10,000 participants were examined and no significant adverse effects were reported. In order to avoid risks, the approval of protocol by the research & ethics committee and Institutional review boards is necessary. Therefore, tDCS safety is limited to standard parameters of stimulation, tDCS equipment and protocols (Kumru et al., 2013; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Zaghi, Thiele, Pimentel, Pimentel, & Fregni, 2011).

1.8 Multimodal Integration

Our everyday life consists of an uninterrupted interaction between arriving sensory information from different senses and departing plans executed by motor activity. Predominantly during aim intended for monitoring behaviour, several circuits of the brain are merging sensory and motor signals. The integration of sensory modalities is significant for cross modal stimuli exploration. To date, Neuroscientists don’t have complete knowledge of how processes of fusion, generalization and convergence across sensory modalities are realized, though much thought has been focused to this problem (Battaglia, Jacobs, & Aslin, 2003; Bolognini & Maravita, 2012; Ernst, 2005; Ernst & Banks, 2002; Fetsch, Deangelis, & Angelaki, 2013).

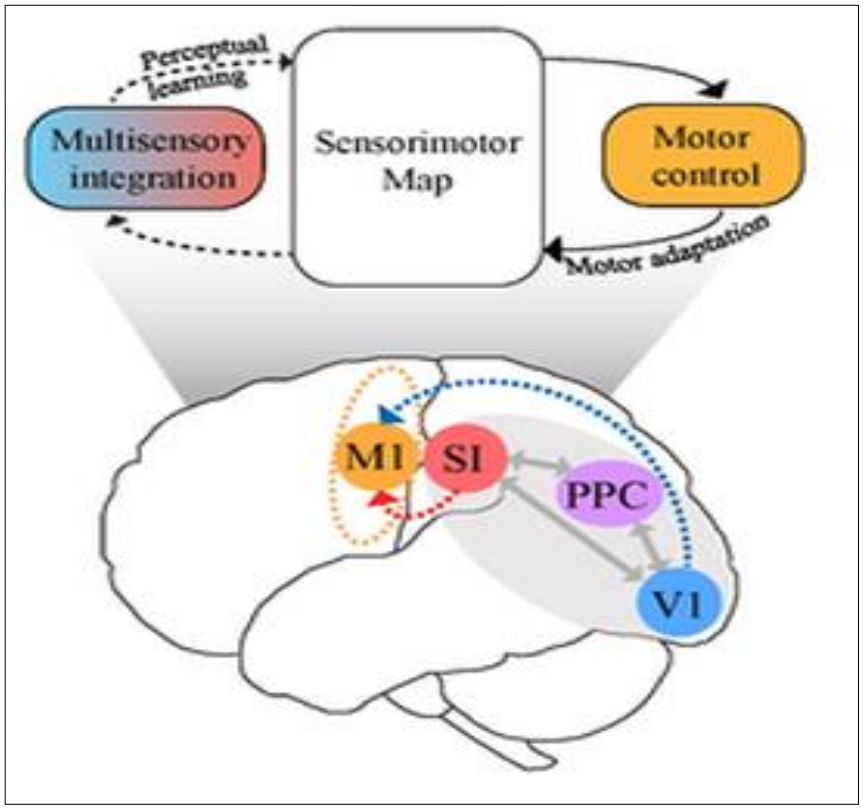


*Figure 1.12- **Multisensory integration map.**The information coming from different sensory regions primary motor area (M1), primary somatosensory area (S1) and primary auditory areas (V1) converge into Posterior parietal cortex before the execution of specific functions.*

It is not sufficient to check the concurrence of areas triggered by two or more dissimilar uni-modal stimuli, in order to investigate a brain area in which neurons receive converging multi sensory signals. One of the previously mentioned studies have shown that multi sensory regions of the brain tends to have a combination of unimodally responsive neurons as well as those driven by unlike modalities. Another hopeful finding from recent neuro-imaging research in humans is that the brain regions activated during a given task and perhaps the multi sensory interactions working within them may be comparable to those recognized as a single unit recording.

1.9 Posterior Parietal Somatosensory Cortex

The Posterior parietal cortex "PPC" is located caudal to somatosensory cortex rostral to secondary and primary visual cortex and it receives input from three sensory modalities: the visual system, the somatosensory system and the auditory system. PPC can be divided into

two large regions, a posterior division with inputs from a collection of higher visual areas, and rostral division with inputs from high order somatosenosry areas.

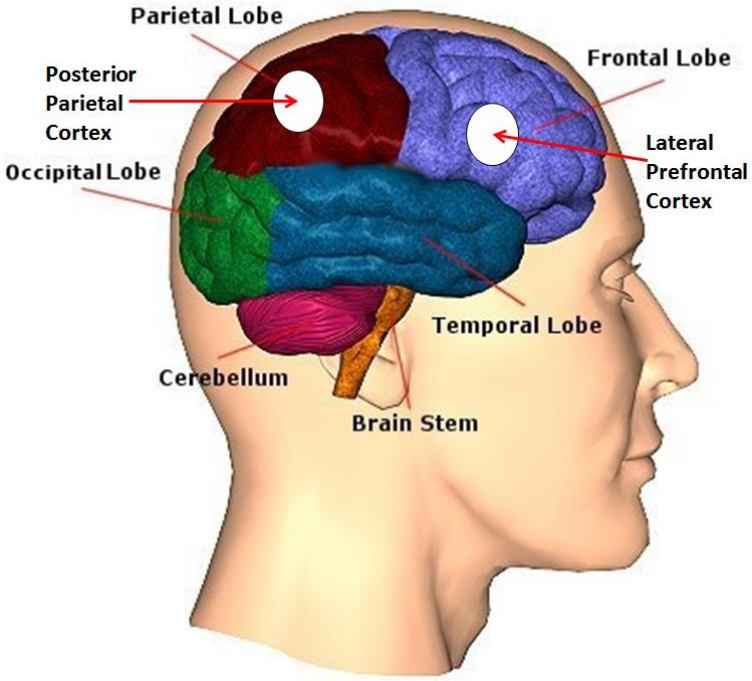


Figure 1.13- ***Locality of Posterior Parietal Cortex.*** *Posterior parietal cortex is an area located in between the primary sensory cortical areas for audition, touch and vision. It a sensory association area and it interprets information form sensory modalities.*

1.10 PPC as a Hub of Multisensory Integration

Our experience of the world generally depends upon integration of signals via multiple senses. In several cases, when we recognize an object independently of any sensory modality, by which we attain the sensory signal, indicates that our knowledge about the things can be accessed and elicited through various sensory pathway. (Nikbakht, Tafreshiha, Zoccolan, & Diamond, 2018; Quiroga, Reddy, Kreiman, Koch, & Fried, 2005). Posterior parietal cortexis a classical association area is known for its properties related to multiple senses, where the basic information from different senses actually converges. It is for that reason not possible to feature PPC to one exclusive computational task. PPC receives information from different sensory areas and a variety of other regions of the brain and is thought to integrate that information to facilitate the execution of functions that entail diverse information. That is why it is associated with higher order functions (Akrami, Kopec, Diamond, & Brody, 2018; Nikbakht et al., 2018). In a recent study published in Neuron, researchers at International school of advances studies (SISSA) probed how the signals coming from the multiple senses

are integrated. It was inferred that the two or three sensory work together more efficiently to generate a better representation of stimuli and the neuronal activity was measure in PPC (Nikbakht et al., 2018). Figure 1.13 illustrates the role of PPC in multisensory stimuli convergence. The information from three sensory modalities (audition, touch stimuli and vision stumli) enter the brain through primary Somatosensory cortex (S1) and primary auditory,cortex primary visual cortex (V1respectively, and converges in the posterior parietal cortex before the execution of the relevant functions.

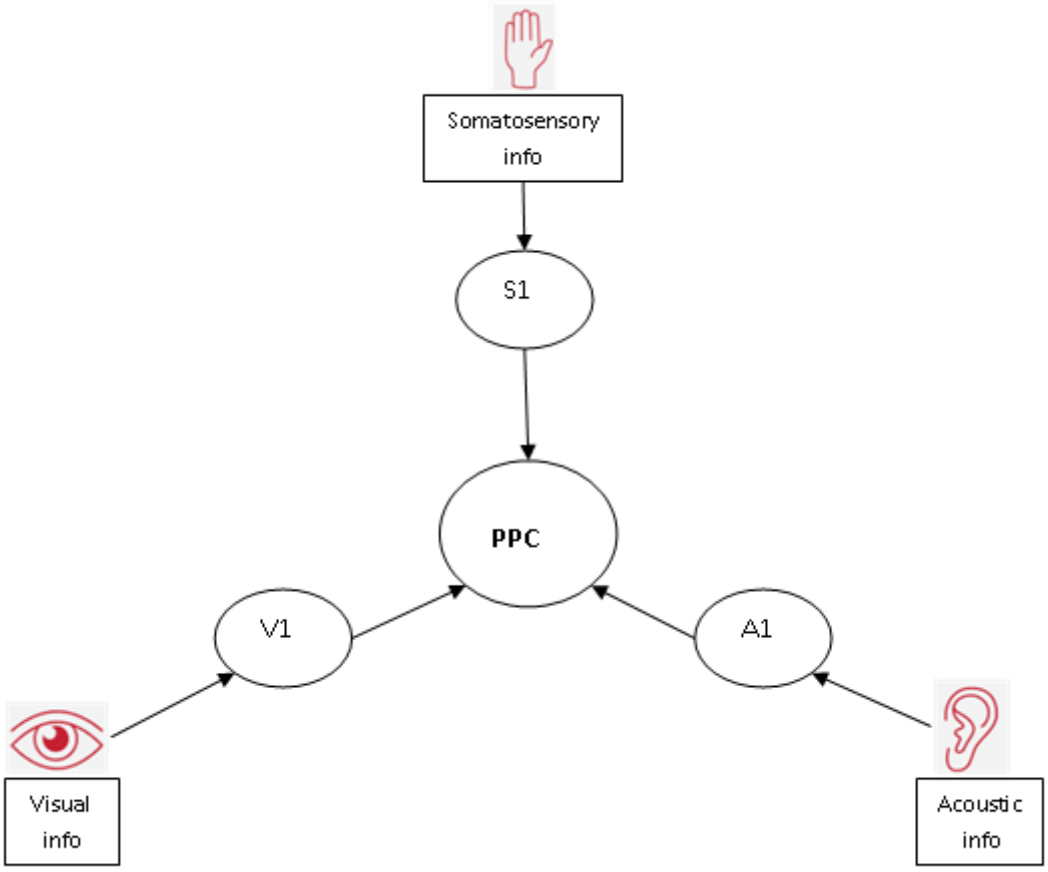


Figure 1.14- ***Merging of sensory information from trimodal senses to the affector-posterior parietal cortex.*** *Acoustic information coming from ear to A1, visual information coming from eye to V1 and Somatosensory information from hand to S1 actually merges into PPC* (Romero Lauro et al., 2014).

2 LITERATURE REVIEW

2.1 Cross Modal Illusory Percept

Numerous neuroimaging studies have identified putative cortical areas including primary and sensory auditory cortices, occipital cortex superior temporal sulcus that are active during the illusions such as McGurk effect (Marques, Lapenta, Merabet, Bolognini, & Boggio, 2014). One of the greatest influential illustrations of multisensory perception is sound based flash illusion formulated by Shams and his collaborators. As a single flash is accompanied by one or more beeps, it is often perceived as two or flashes being perceived, named as fission illusion. A subsequent fusion illusion is when a single beep causes flash stimulus to be perceived as two. These persuasive multisensory phenomenons underline how sensory specific perceptual judgment with reference to one sense can significantly be affected by associations with another sense.

Verification from imaging studies on human brain signifies that the relations between polysensory (two or more senses are involved) and visual cortical may possibly represents the neural substrate for the production of the flash illusion induced by sound. ERPs and MEG studies demonstrated a modulation of doings in occipital, parietal and temporal cranium locations, illusory effects were experienced by the subjects (G a Calvert, 2001; Niedermeyer & Lopes da Silva, 2005).

2.2 Visual-tactile Integration

One of the findings suggests that visual cortices are intimately involved in processing certain type of tactile data in normally sighted subjects. The precise nature of and limits on such cross-modal interactions remain unclear (Qin & Yu, 2013). Many research studies have reported the involvement of visual areas in a series of tactile processing for tactile perception (Ricciardi et al., 2007, 2011).

Most multisensory studies have focused on connections between audition and vision, appealing phenomenon involving interactions between somatosensory and additional modalities have lately been reported too (Violentyev, Shimojo, & Shams, 2005).

Hotting and Roder (Hötting & Röder, 2004), reported an equivalent of flash illusion induced by sound in the audio-tactile field, signifying that auditory stimulus can drastically modify the sensitivity of tactile stimulus.

Hence, the end result of this research suggests a powerful modulation of visual perception by tactile stimulus and the perception of the tactile stimulus can be modified by the visual stimulus. Lately, neuro-anatomical pathways have been acknowledged, interceding the direct modulation of visual processing from the auditory cortex and exciting the superior temporal poly sensory areas of the brain indirectly (Lacey & Sathian, 2015; Rockland & Ojima, 2003) No pathways have thus far been known connecting the visual cortex to somatosensory. It is promising that the practical flash illusion induced by the touch is the consequence of exchanging the visual and tactile contributions in higher associative cortical areas' order of the brain. Conversely, flash illusion induced by the sound has currently been revealed, linking the modulation in the premature visual cortex (Lange, Oostenveld, & Fries, 2011; L. Shams, Kamitani, Thompson, & Shimojo, 2001; Ladan Shams, Iwaki, Chawla, & Bhattacharya, 2005;Bhattacharya, Shams, & Shimojo, 2002). Similar evidence properties have deduced that the illusions induced by the sound and touch are alike in perception. For instance, in the sound induced flash illusion, an effect of fusion was found. Fusion illusion is when the single flash followed by the two tactile-touches perceived as two flashes. This effect tends to be stronger than the fusion effect. Fusion effect is when the single tap is perceived as a single flash. Hence, it is likely that they involve comparable neural processes. Hence, the touch induced flash illusion may possibly be involved in the modulating the activity in the visual cortex.

Prior consequences based on imaging techniques are dependable with this suggestion of untimely visual and tactile interactions. Another research has demonstrated that the tactile stimulation can alter action in the occipital regions of the brain in addition to multimodal (intar paraietal sulcus) regions and somatosensory (post central gyrus) and (E. Macaluso, Frith, & Driver, 2001).

2.3 Sensory- perceptual processing with tDCS

The quantity of rehabilitation and sensory processing using tDCS has been increasing importance in the fields of research and rehabilitation. Currently many investigations are going on in the fields of sensory possibilities and possibilities for its use in treatments. The sensory information coming from different modalities, actually merge in a common region of

our brain before it is executed by the effectors. This continual process of integration and merging of senses is done by posterior parietal cortex.Several recent studies (Ga Calvert, Campbell, & Brammer, 2000; Foxe et al., 2000; Giard & Peronnet, 1999; Lewis, Beauchamp, & DeYoe, 2000; Raij, Uutela, & Hari, 2000) in humans using fMRI (Functional magnetic resonance imaging), ERP even- related potentials) and MEG (magnetoencephalography) have used the same approach by identifying the brain regions that show multiplicative interaction in response to multimodal tDCS stimulation.

2.4 Audio-visual Integration with tDCS

Perceptual effects on tDCS on intricate perceptual phenomenon have also been investigated. A group in Italy pioneered the multisensory integration research monitoring tDCS effects over posterior parietal cortex (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010). There was an increase in spatial orientation in healthy human participants examined before and the effects of administered over rPPC (right posterior parietal cortex) in a task using video, audio and bimodal audiovisual stimuli as well. Extending the previous knowledge, tDCS studies on right PPC have considerably enhanced the processing of unimodal visual and auditory stimuli. Hence by down regulating or up- regulating the excitability of brain by tDCScathodal or anodal respectively on PPC appears to be a novel approach for enhancing multisensory and unisensory crossodal stimulation (Emiliano Macaluso & Driver, 2005; Rizzolatti & Matelli, 2003; Weiss et al., 2013). The excitatory effect of anodal PPC greatly enhanced the response of unimodal stimuli, this may possibly be effective in generating a stepping up of response to bimodal stimuli.

It is important that tDCS findings verified PPC contribution in specific tasks and even though PPC is considered as an associative area, it doesn't seem to be essential in other tasks merging audiovisual information. The reason might be the placement of montages used for enhancement of task performance.

2.5 tDCS affecting cross modal illusory percept

The idea of sound based visual (fission and fusion) illusion and tactile illusion is one of the most dominant illustrations of multisensory perception which is adapted from the original research of Shams (Ladan Shams, Kamitani, & Shimojo, 2002). Using this audiovisual illusion, researchers have explored the likelihood of excite or inhibit the multisensory perception by modulating relevant cortical areas with tDCS, which mediated the audio-visual interactions (Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011a). These

modulatory effects greatly depends upon the stimulation parameters which include the stimulated area, the current density, current polarity, the type of evoked multi sensory percept (fusion vs. fission illusion). By changing the polarity and placement of montages, different results can be deduced. Hence, by decreasing or increasing the modulation of temporal and occipital areas of the brain by tDCS can possibly manipulate the multisensory interaction involving both auditory and visual modalities.

2.6 Trimodal integration with tDCS

The results from various research suggests that tDCS may possibly be a hopeful tool to progress performance in tasks that entail multisensory auditory-visual, visuo-tactile visuo-motor, visuospatial and integration. Studies on cross modal connections have mainly established such additive/facilitatory effects (G a Calvert, 2001; Gemma Calvert, Spence, & Stein, 2004; King & Calvert, 2001) and presume that every kind of sensory information is separately sent from primary sensory regions to some higher to some higher sensory association regions to be integrated (Driver & Noesselt, 2008). Sound based flash illusion and vision based tactile illusions clearly demonstrate that tDCS can quantitatively alter the visual and tactile perception induced by sound (Violentyev et al., 2005) and therefore, there is a hope to get novel insights into the mechanisms involved in the multimodal integration of perceptual information.

2.7 Thesis Overview

The tDCS is a neuromodulatory mechanism which elicits the action potentials in cortical neuron and is responsible for cognitive improvements. Posterior parietal cortex (PPC) is a heteromodal area of convergence of sensory modalities, consisting of uni and multi sensory neurons which results in improvement via tDCS interventions in diverse sensory modalities and neurons which integrate converging sensory organization (Emiliano Macaluso & Driver, 2005). Posterior Parietal Cortex is an ultimate area for multisensory integration and synchronize alterations essential to exchange sensory input to effectors output. The neuromodulation studies have shown the effects of tDCS focusing right PPC on bi-modal interactions e.g. audio-visual integration, visuo-motor integration but a very lesser research is done in modulating tri-modal integration with tDCS. (Bolognini et al., 2011a; Marques et al., 2014).

The aims and objectives of this study were;

- To determine the functional contribution of posterior parietal cortex in the generation of integrative effect of trimodal stimuli
- To investigate the interaction of visual, auditory and tactile modalities for the perception of succession of trials.
- To estimate the effect of bipolar bi-parietal Transcranial direct current stimulation on the perceptual processing of audio-visual-tactile sensory combinations, through a numerosity judgment task.

3 MATERIALS AND METHODS

3.1 Study Protocol

A double blinded, randomized and sham controlled design is employed to investigate the effect of tDCS targeting cathodal, anodal and sham PPC on trimodal integration underlined by multisensory integration process in healthy participants. An experimental task of auditory, visual and tactile stimulations was designed to check the modulation of tDCS in the 3 different sessions. The data was acquired and analysis was done.

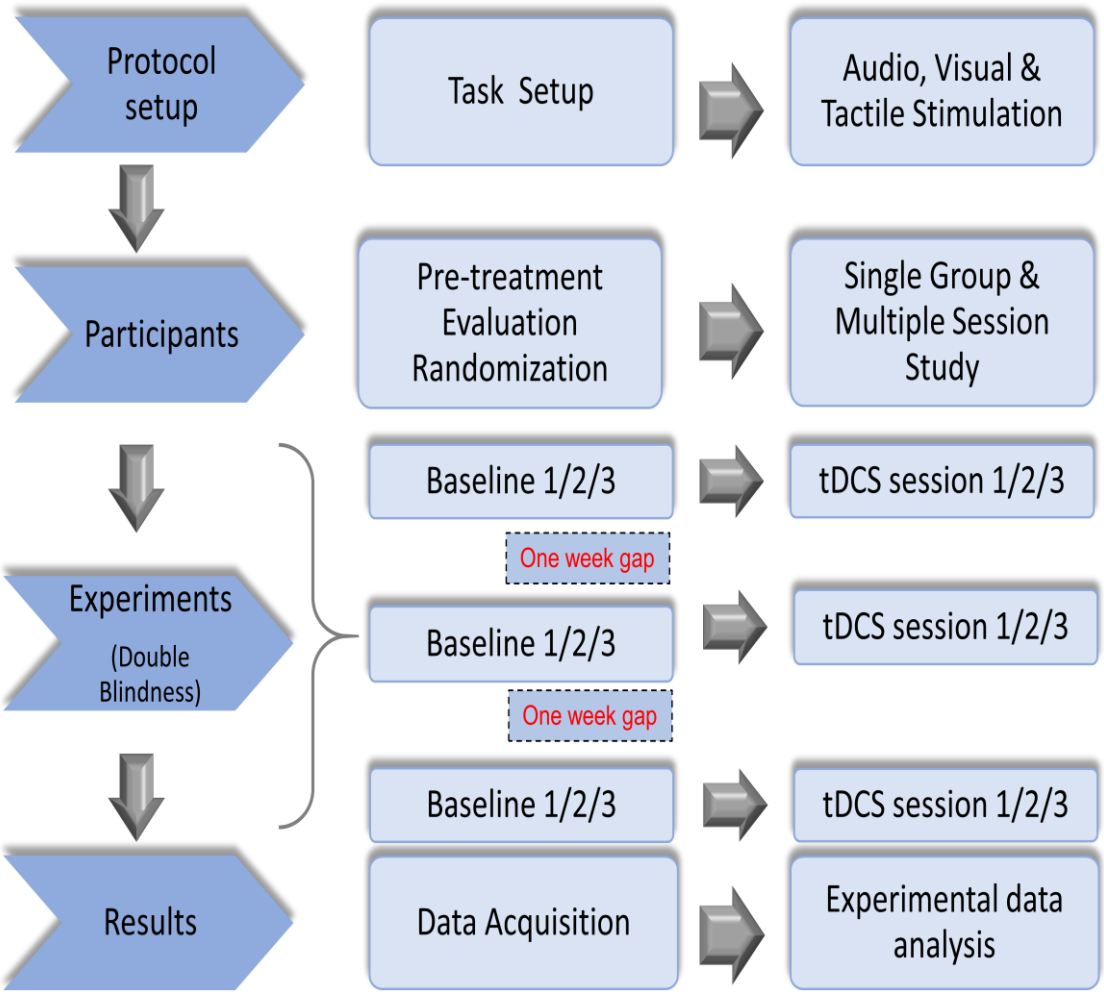


*Figure 3.1- **Study Design***

3.2 Setup and Software

Auditory, Visual and Tactile Stimuli were programmed in Matlab (2015a 64-Bit) using Psychtoolbox (Nava, Grassi, & Turati, 2016). Tactile stimulator was interfaced with the System via Serial port.

*Table 3.1- **Requirements of Software and Hardware***

Software	Hardware	Data Acquisition & Statistical Analysis
• **Matlab (2015a 64-Bit)** • **Psychtoolbox for Matlab**	• **System** (square monitor, resolution 1280 x 1024,refresh rate 75 Hz). • **Tactile stimulator** • **Power Lab** • **HD Headphones: A4 Tech HS-800** (built-in Sound) • **tDCS device**	• **Lab Chart 8** • **Excel Sheet** • **Google forms** • **Post- Experiment Experience** • **Statistica**

3.3 Spatiotemporal profile of Auditory Stimulus

Built-in Sound of the Computer is used to generate the auditory stimulus. It is a tone of 4.5 kHz frequency, presented for 13ms, 1 or 2 times. Over Ear full sized headphones, A4 Tech Hs-800 was used as shown in the Figure 3.2. (Ladan Shams et al., 2002)

*Figure 3.2- **A4 Tech –HS800 wired - over the ear - headphones***

3.4 Spatiotemporal profile of Visual Stimulus

The visual stimulus consisted of a uniform white disc with luminance 120cd/m^2, 2 degree in diameter and was presented for 13ms, 1 or 2 times.

Every trial initiated with the presentation of a grey fixation cross (luminance 7cd/m^2) 5 deg below the disc being flashed, displayed on a computer screen (resolution 1280 x 1024,refresh rate 75 Hz) with black background. Subjectswere asked to maintain fixation on this cross throughout the entire experiment (Figure 3.3)(Ladan Shams et al., 2002).

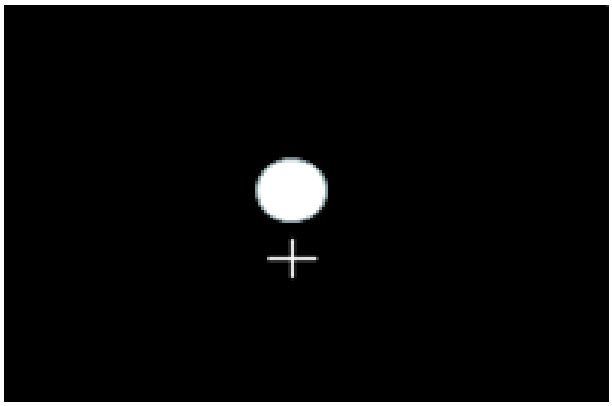


Figure 3.3- ***Pictorial representation of Flash & Fixation cross***

3.4.1.1 Visual Angle Calculation:

The visual angle isto determine the size of the object's image on the retina. This visual angle depends on the distance between the observer and the object being seen as well as the object's size. Larger the distance between the two, smaller will be the visual angles. Conversely, larger the object to be seen, larger will be the visual angle.

Visual angle was calculate by this formula,

$$\boldsymbol{D = \frac{2\pi dA}{360}}$$

Where, d is the distance between the object and the observer, A is the visual angle, D is the diameter of the object as shown in the figure 3.4. We used d= 57cm, D=2.5cm, Hence A=2 degree visual angle

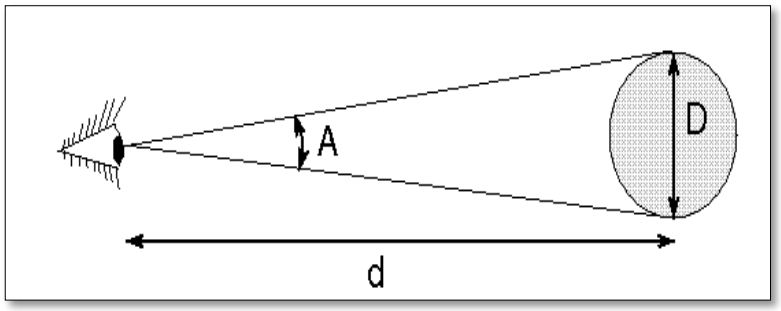


Figure 3.4- ***Visual Angle for calculating the diameter of the flash.***

3.5 Spatiotemporal profile of Tactile Stimulus

Tactile stimulation was given through a solenoid based stimulator, driven by custom–built electronic circuitry. For tactile stimulation, the pin was attached to the end of pull-push solenoid (Geeplus,M-110C). This pin was lifted by 2mm, through the hole of the box as shown in the figure 3.5, and stayed elevated and touches the right index finger for 13ms, 1 or 2 times and then was lowered again for 65ms (Violentyev et al., 2005).

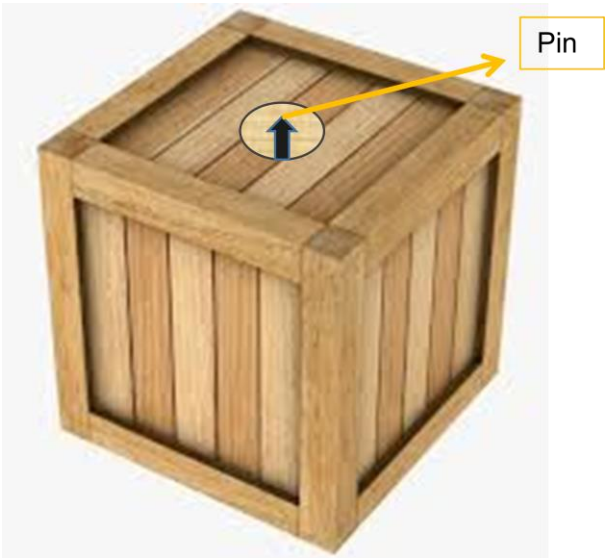


Figure 3.5- ***Tactile Stimulator.*** *The pin is elevated through the hole and touches the index finger of the participant.*

3.5.1.1 Schematics and Circuitry

The circuitry for tactile simulator was made in Proteus 8 to make the schematics and printed circuit-board (PCB) layout and then PCB was designed (Figure 3.6). The components: NPN Transistor NEC 882, Resistor of 1k ohm, Diode, Pull-push solenoid and

Serial port were used for making the circuitry. The diode was used in parallel with the pull-push solenoid for the protection of transistor. When a DC signal was given to the base of the transistor, through serial communication to RTS (request to sent) pin of Serial port and the collector is powered up by 44V power supply, then the solenoid is turned on and off with the help of defined protocol/Matlab code (Figure 3.7).Table 3.2 shows the parameters used in all designing the task.

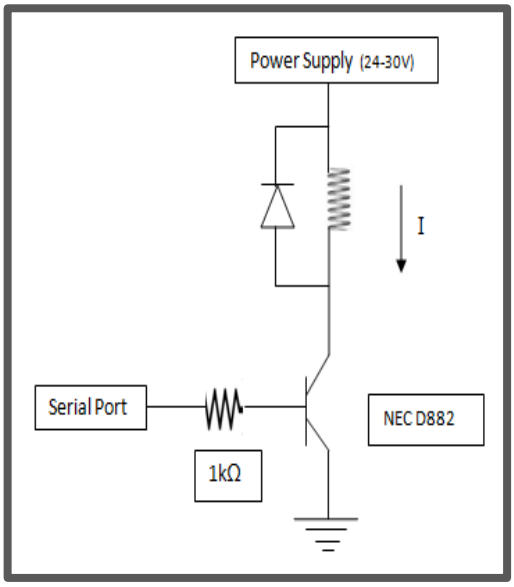


Figure 3.6- ***Schematics of Tactile Stimulator***

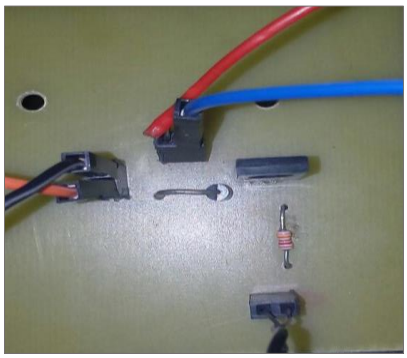


Figure 3.7- ***PCB Circuit for Tactile Stimulator***

Table 3.2- ***Summary of Stimuli Presentation***

Spatiotemporal Profile of Visual Stimulus	
Luminance of a uniform white disc	120cd/m^2 (40% of 300 cd/m^2)
Diameter of the white Disc	2deg
Luminance of a white fixation cross	7cd/m^2
Distance between disc and fixation cross	5 degree above fixation point
Duration of flashes	10 ms
Separation between 2 flashes	50 ms
Separation between 1st flash & Beep	20 ms
Spatiotemporal Profile of Auditory Stimulus	
Frequency of beep/s	3.5 kHz
Duration of beeps	10 ms
Duration between the beeps	50 ms
Spatiotemporal Profile of Tactile Stimulus	
Duration of taps	10 ms
Duration between 2 taps	50ms

3.6 Task Setup

The task setup is a combination of congruent and incongruent auditory, visual and tactile stimulation.(Wozny, Beierholm, & Shams, 2008). Congruent conditions are those in which the number of beeps, taps and flashes are equal in number. Whereas, Incongruent conditions are those in which the number of beeps, taps and flashes are not equal in number.

3.6.1 Block Design

There are total of 15 blocks and each block has 6 no. of conditions (trials), each block is randomized & has the same number of similar combinations of stimuli.Each condition will be repeated 15 times, designed for a total of 90 trials, in an arbitrary order.

3.6.2 Catch trials

Catch trials were randomly introduced in the total of 90 trials (i.e. 6 catch trials + 84 trials = 90 trials). One extra beep was introduced in the each catch trial.

There are total of 6 catch trials per condition in each block. The catch trials are not repeated, one combination of catch trial will be in one block. The total no. of blocks are 15, with the randomization of 6 conditions, none of the combination of trials is repeated. The no. of combination of block is being perceived.

Table 3.3- ***Block Design showing block numbers, consisting of catch trials***

No Catch Trails					**Catch Trials**						**No Catch Trails**			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

3.6.3 Stimuli combinations

The primary beep was tagged along by the initial flash subsequent to 26miliseconds. In addition to this, the gap (stimulus onset asynchrony, SOA) was 50ms, among the flashes, beeps and taps. The relative timing of the each stimulus was tuned in such an approach that the middle of each stimulus coincides with the time to the middle of other modalities. The number of auditory stimulus was fixed, while the number of visual and tactile stimuli could be one or two. Thus, the total number of combinations is 6, including the congruent as well as the incongruent conditions (Wozny et al., 2008).

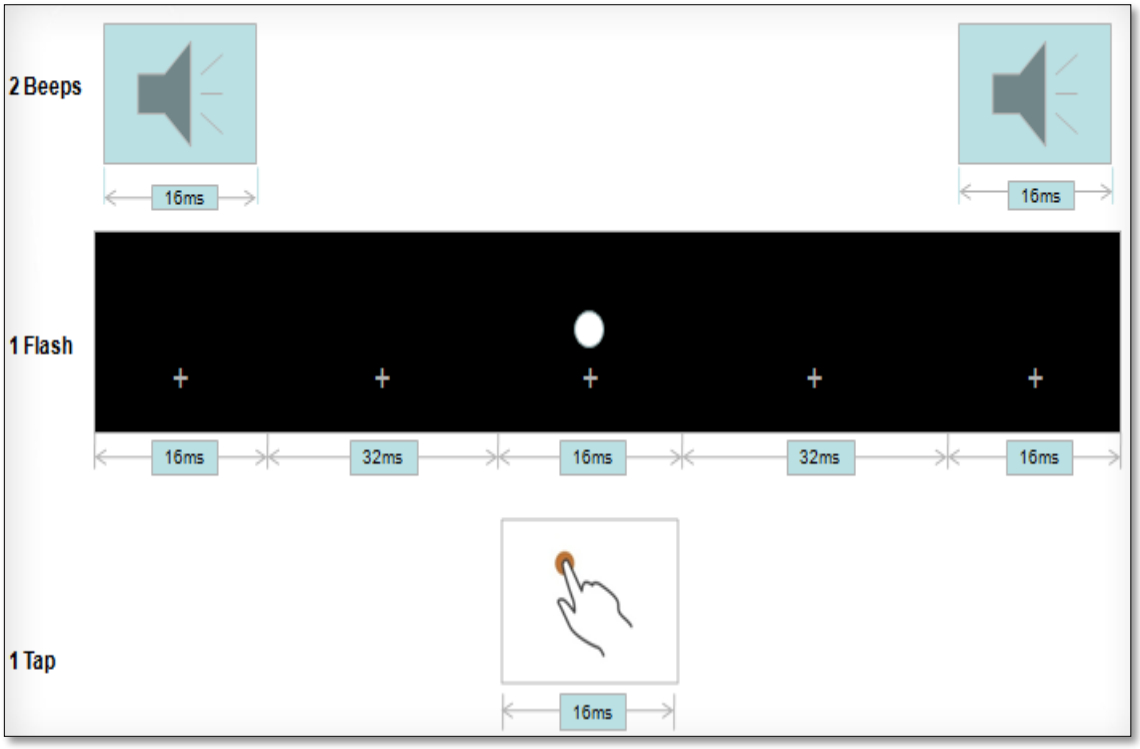


Figure 3.8- ***Presentation of one stimuli trial with 2 beeps, one flash and one tap (T)***

3.6.4 Trials

Following are the Trials with 6 conditions (T1-T6). Beep, two in number, is fixed throughout the task, while the number of Flashes (1/2) and Taps (1/2) are variable.

Table 3.4- ***Congruent (t4) and Incongruent Trials (T1, T2, T3, T5, T6)***

Trials	Combinations
T1	Beep Flash+TapBeep
T2	Beep Flash+Tap BeepTap
T3	BeepFlashBeepFlash+Tap
T4	Beep Flash+Tap BeepFlash+Tap
T5	Beep Flash+Tap BeepFlash
T6	Beep Tap Beep Flash+Tap

3.7 Participants

Out of 28 participants underwent the screening procedure and 23 (12 females, 11 males (age:25±3) right-handed participants were selected and completed the study. 5 subjects were excluded from the study.

3.7.1 Recruitment

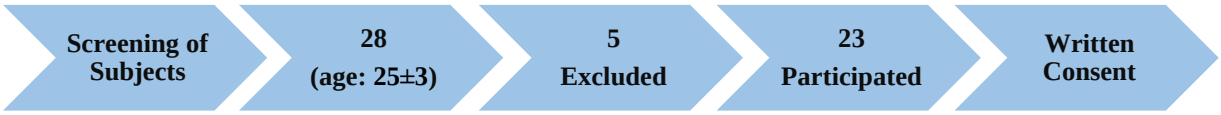


*Figure 3.9- **Recruitment process of the participants***

3.7.2 Inclusion Criteria

Participants were selected after complete analysis of the screening form being filled before their selection for the experiment(Woods et al., 2016). Each selected participant had normal or corrected-to-normal vision and typical hearing and had no current history of medication or neuropsychological disorder (last 3 months) (Violentyev et al., 2005).

3.7.3 Exclusion Criteria

Exclusion criteria were concomitant medication expected to affect mental performance, current history of medication or dependence in the previous 3 months, any psychiatric disorder, recent history of stroke,head injury or seizure(Martin et al., 2014). In according with the current study, Subjects suffering from diseases (depression, migraine, frequent headaches, Dyslexia) and those who were currently (within 3 months) on medication (Inderal, Toparamate, Lexotanil, Zyrtec and Loratidine) were excluded, which can affect our study (Boggio et al., 2008).

3.7.4 Ethics Statement

All experiments performed were in compliance with the rulings of the Declaration of Helsinki (Wright & Krekelberg, 2014). The protocol was approved from the SMME Ethics Committee, NUST. Informed consent in written for was taken from all recruited subjects former to the start of study.

3.8 Transcranial Direct Current Stimulation (tDCS) Device

The anodal, cathodal and sham stimulation was given to all subjects under study. Transcranial direct current stimulation was administered by a device which is driven via battery. This device is a caputron based Activadose II Iontophoresis Deliver Unit, (https://www.caputron.com/transcutaneous-electrical-stimulation/333-activadose-ii-starter-kit.html), a continuous current stimulator by by means of a pair saline-soaked sponge electrodes (Figure 3.13). In accordance with the safety guidelines, a steady current of 2mA intensity in a ramp up manner with an adjustable duration (14min for anodal/cathodal tDCS and 1 min for sham tDCS) was applied on the scalp (Poreisz et al., 2007). Electrodes were placed on the scalp on P3 and P4 with the help of the caputron head band. A metal mesh was enclosed by a rubber material, constitute the electrode. Sponge inserts were placed inside the rubber electrodes and were evenly soaked in a 0.9% saline solution and banana clips were inserted before desired electrodes being applied on the scalp as shown in the figure 3.14 (Wright & Krekelberg, 2014).

Figure 3.10- ***Kit of Activadose ii***

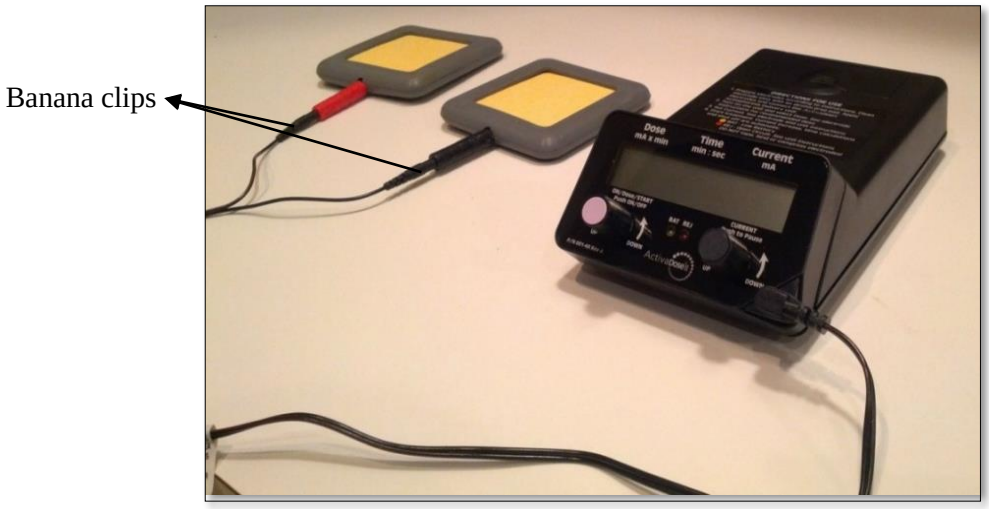


Figure 3.11- ***Activadose ii with the positive (red) and a negative (black) electrode***

3.8.1 tDCS Dosage

The saline soaked sponges were inserted in square shaped rubber electrodes with an area of 25cm^2 prior to administering tDCS dosage to the participants. The current applied was 2miliamperes for duration of 14 min.

Table 3.5- ***Stimulation parameters administered for Active tDCS Intervention***

Stimulation from Activadose ii							
Type of Stimulation	**Shape of Electrodes**	**Electrodes Insert**	**Area**	**Material**	**Current**	**Duration**	**Dose (Current x Duration)**
tDCS	**Square**	**0.9 % Saline soaked sponge inserts**	**25cm²**	**Rubber Electrodes**	**2mA**	**14 min** **Offline-tDCS: 8min 30sec** **Online-tDCS: 5min 30sec**	**28mA-min**

3.8.2 Type of tDCS Effect

tDCS effect could be assessed during the current flow as well as after the current flow termination. There are three different designs to monitor the effect of tDCS namely; offline, online and mixed design. An online design refers to the method in which the participant completes the task while receiving the stimulation. It is administered to check the direct effect of tDCS. Conversely, an offline design refers to the task and tDCS not undertaken concomitantly and is administered to check the pre and post effects of tDCS (Thair et al., 2017). In this Study Design, mixed design was performed for Pre-During-Post tDCS assessment. Mixed design is the combination of offline and online designs which is used to measure the effect of both the stimulation and the assessment tasks at the same time(Thair et al., 2017).

3.8.3 tDCS Montages

The 10/20 EEG System was used to determine electrodes placement and to localize areas on the cranium. Electrodes were placed over P3 and P4 for targeting Posterior Parietal Cortex (PPC).

3.8.4 Dual tDCS

The Dual tDCSis an integrative type of stimulation, in which no reference electrode is used and both electrodes with opposite polarity are used. It may have the potential to re-balance the deregulated interhemispheric interactions(Lefebvre et al., 2013). For describing electrodes montages, Bipolar–balanced electrodes (Dual tDCS electrodes) were used for concurrently activating a brain area and reducing its contra lateral counterpart. P3 and P4 locations (P3 for anodal electrode placement and P4 for cathodal electrode placement) were used to incease the modulation of the left PPC and to lessen the modulatory effect of right PPC (Wright & Krekelberg, 2014).

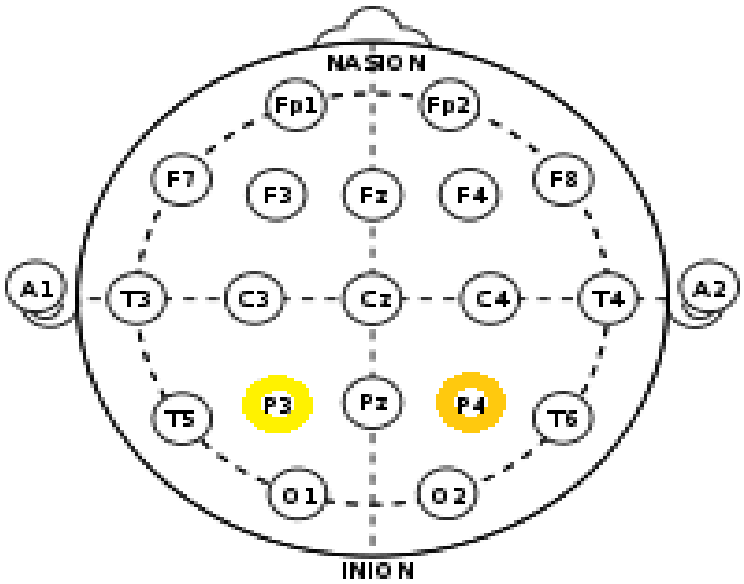


Figure 3.12- ***Bilateral bipolar-balanced tDCS Montage.*** *P3 and P4 are being used in dual tDCS montage, to increase the excitability of the right PPC and to diminish the excitability of left PPC.*

3.8.5 Intervention Types

There are three different types of tDCS interventions given to Participants, Cathodal, Anodal and Sham tDCS as illustrated in the figure 3.18. Every participant performed the task without tDCS and after that they were haphazardly selected to any of the three double-blinded tDCS interventions for one experiment a day. Each experiment was after a gap of one week, which was needed to wash-out the effects of tDCS (K. van Dun, Bodranghien, Mariën, & Manto, 2016; Vannorsdall et al., 2016). For active sessions, the tDCS stimulation was delivered for 14 min. For left cathodal-right anodal stimulation, the anodal electrode was placed on P4 while P3 was targeted for placement of cathodal electrode. For left-anodal / right-cathodal stimulation, the position of electrodes was overturned. Whereas, the Sham intervention session was administered in the same manner as of active sessions, but the current was delivered for 1 min with a ramp up and ramp down time of 30s. The sham generally consists of current being ramped up for 30 seconds, followed by instantaneously ramping down the current for 30 seconds. To make sure that the results are really as a result of stimulation and not typically due to any practice or placebo effect, generally the information is frequently measured by comparing the before and after active and sham sessions. (Thair et al., 2017; van Dun et al., 2016b).

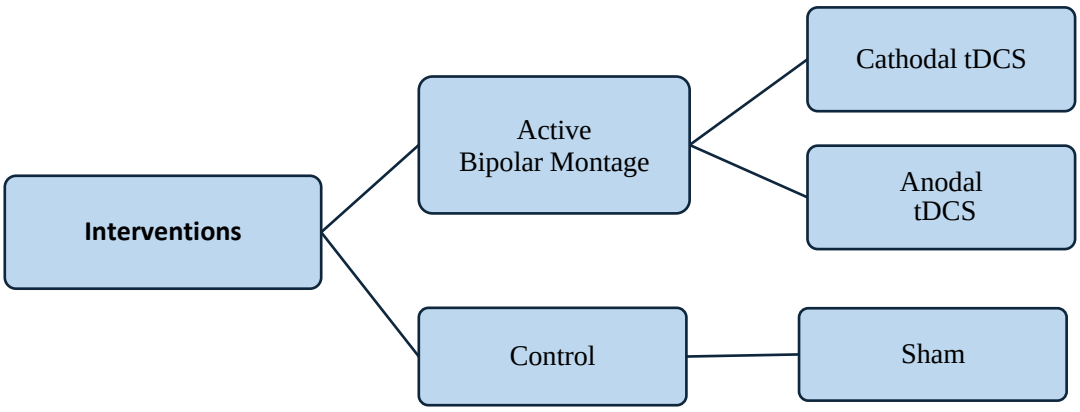


*Figure 3.13- **Types of tDCS Intervention**. Two active interventions, cathodal and anodal tDCS and one control i.e. sham tDCS were administered to all participants with one tDCS session per weeks.*

3.8.6 Blindness

Blindness in a experiment is done in which information about the intervention type is masked from the participant as well as the researcher in order to reduce or eliminate biasness The experiment was double-blinded i.e. the participant as well as the researcher was unaware if they are being given a active treatment or a control treatment(Ruffini & Barcelona, 2013). To blind the participant effectively, the electrodes stay on the cranium even after the current is ramped down during offline tDCS for active or sham stimulation and let the participant wait for the same duration of time as in active intervention just to attain the sense of equivalent session length (Woods et al., 2016).

3.9 Procedure

The screen was placed 70cm in front of the subjects, in order to comfortably view the visual stimulus. Duration of the task was about 15min. The participants were asked to judge the quantity of flashes, observed on screen, the number of beeps perceived through headphone and the number of taps produced by the stimulator(Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011b).

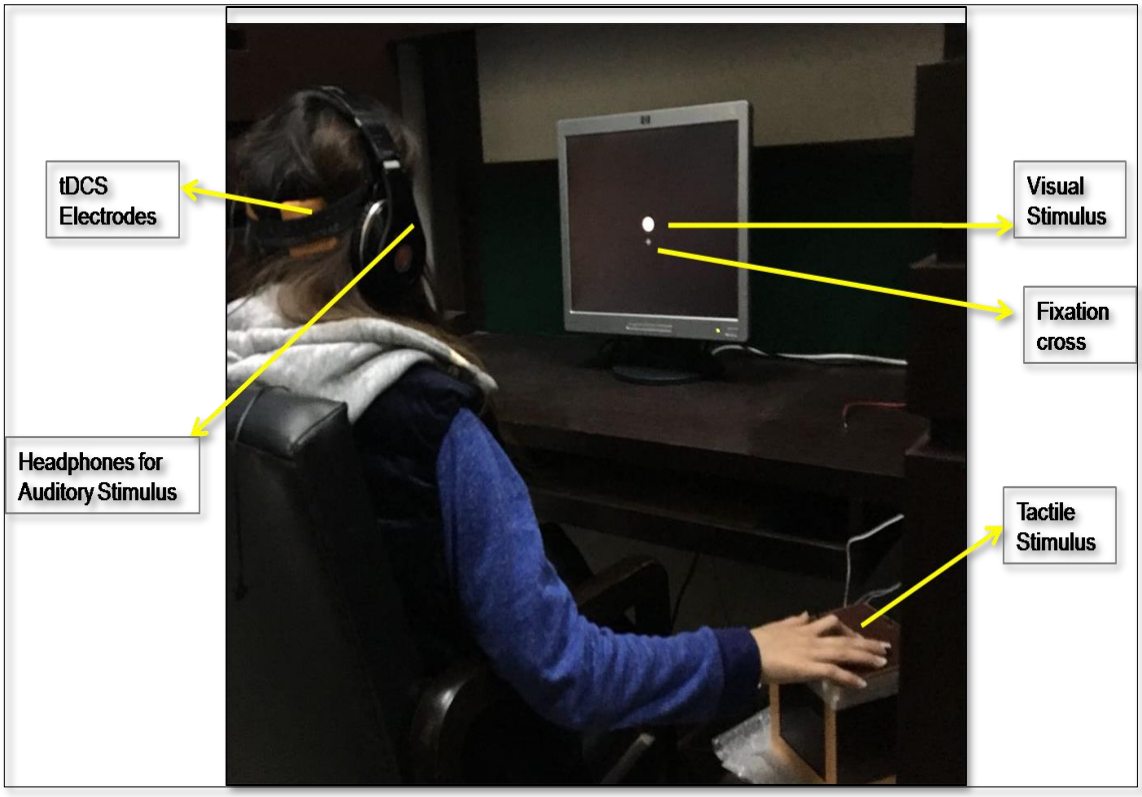


Figure 3.14- ***Subject is ready to perform the task while getting tDCS stimulation***

3.9.1 Test Trials

At the beginning of the first session only on the first day, 12 practice trials (2 trials per condition) were administered so that the participant could get familiar with the kind of task being performed and how each trial is to be answered in duration of 5 seconds. These trials were not included in the subsequent analysis(Bolognini et al., 2011b).

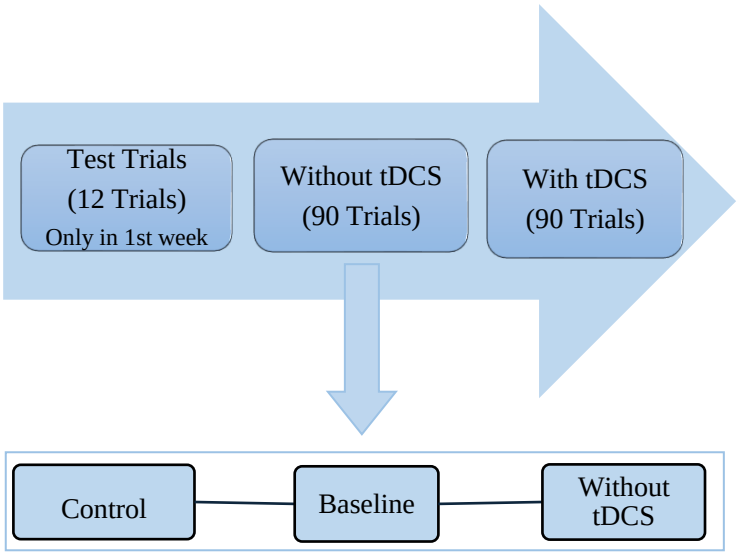
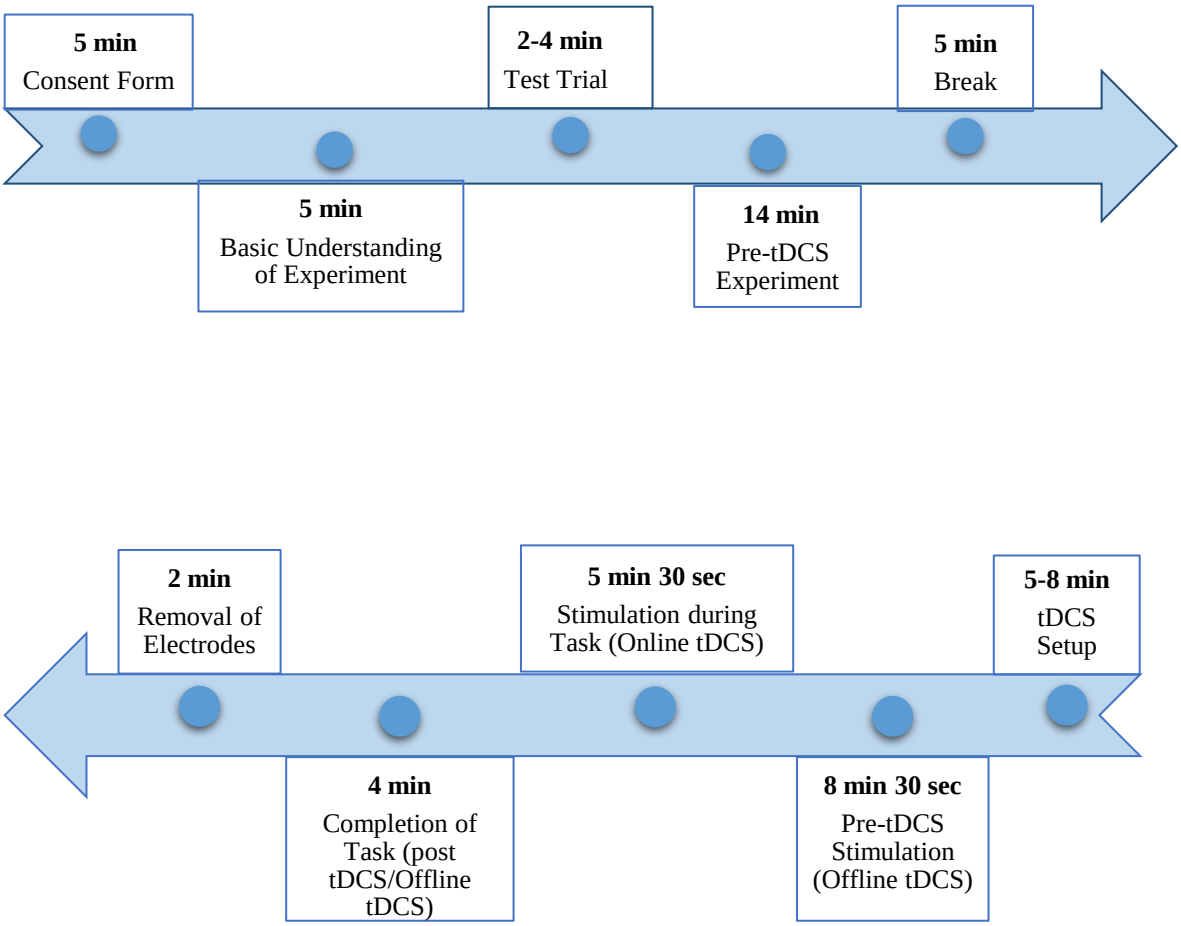


Figure 3.15- ***Week 1 trials; Test Trials are performed by the participants only in week 1***

3.9.2 Duration of Experiment

Starting from signing the consent form to the end of the session, the total time required for the Experiment is 1 hour approx.

*Table 3.6- **Distribution of time for 1 experiment each week.** From start to the end, the total time taken to complete a session per day is approximately 1 hour.*



3.10 Post-Experiment Questionnaire

At the end of the session on 3rd week, every participant was asked to fill the form; Post Experiment Questionnaire to describe the levels of itching, numbness, pain and tingling at stimulation site, headache, discomfort, burning sensation, mild nausea, fatigue, nervousness, sleepiness and difficulty in concentrating experienced in all experiments by using a numeric rating scale to demonstrate the possible influence of psychological condition on the outcome measures (range 1-5, where 1= not at all & 5=unbearable) (Andre R Brunoni et al., 2013; Andre Russowsky Brunoni et al., 2011)

Secondly, in order to insure that the participants were effectively blinded, they were inquired about the kind of stimulation they think they received each week.

3.11 Responses of the Participants

The number of correct responses were recorded in each session with the help of excel sheets manually as well as Google forms.

3.12 Statistical analysis

Statistical analysis was done on Statistica. Repeated measure anova ($ANOVA_{RM}$) was employed to check the effect of the types of intervention of tDCS and for finding significant differences between the baselines and tDCS intervention. The 3 baselines as well as the pre and the post stimulation results were also compared. The data was statistically evaluated for significance employing Repeated Measures Anova, which is followed by Tukey's multiple comparisons test for checking the relative significance among the groups.Values of less than 0.05 were regarded as significant.

4 RESULTS

Transcranial Direct Current Stimulation was investigated for its effect on trimodal integration, stimulating and inhibiting right Posterior Parietal Cortex. The assessment was done by measuring the number of Correct Responses of 90 trials pre and with tDCS in each session per week. The study was purposely was a double blinded and sham-controlled. Repeated measures ANOVA was applied to the pre as well as with tDCS sessions and the results are as follows.

4.1 Normality test

For assessing whether the data is normally distributed or not, Shapiro-Wilk Test was done. The probabilities of all sessions are greater than 0.05, hence the data of the 3 weeks was normal which means that the data is not different from normal. Figure 4.1-4.6 shows the normality test done on the data of 3 weeks for checking the normality.

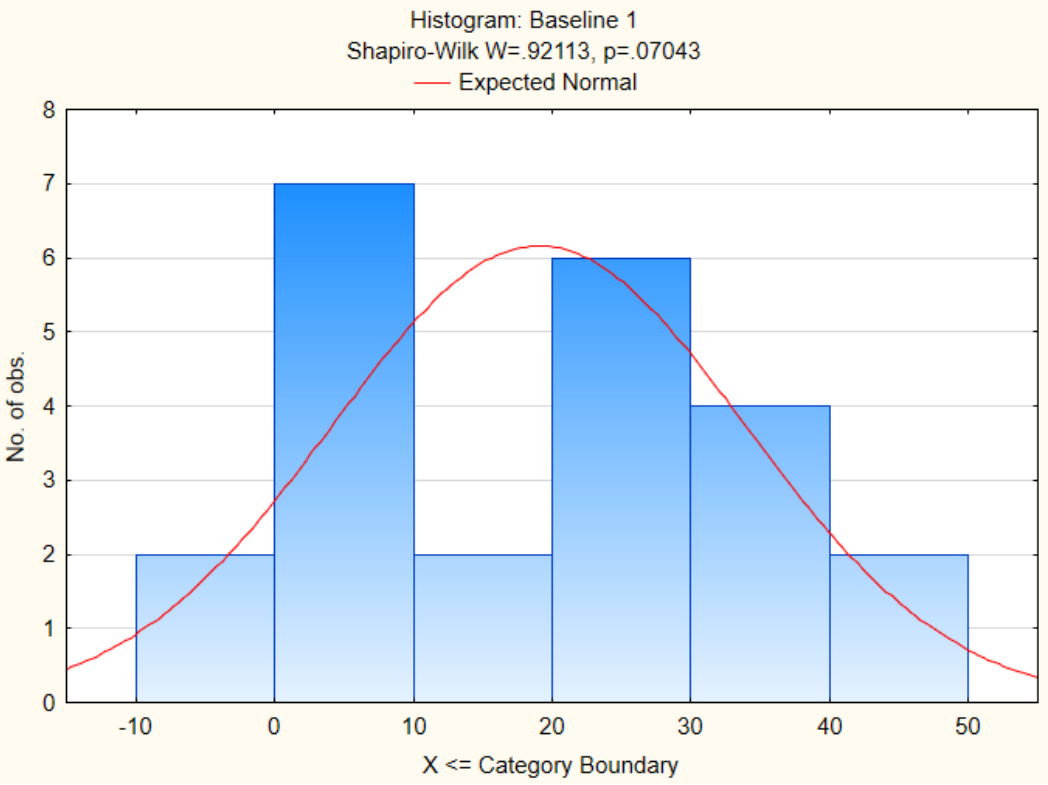


Figure 4.1- ***Graph for the results of Shapiro-Wilk test for Baseline 1.*** *The graph shows thatthe data is not different in from normal and the p value is 0.07*

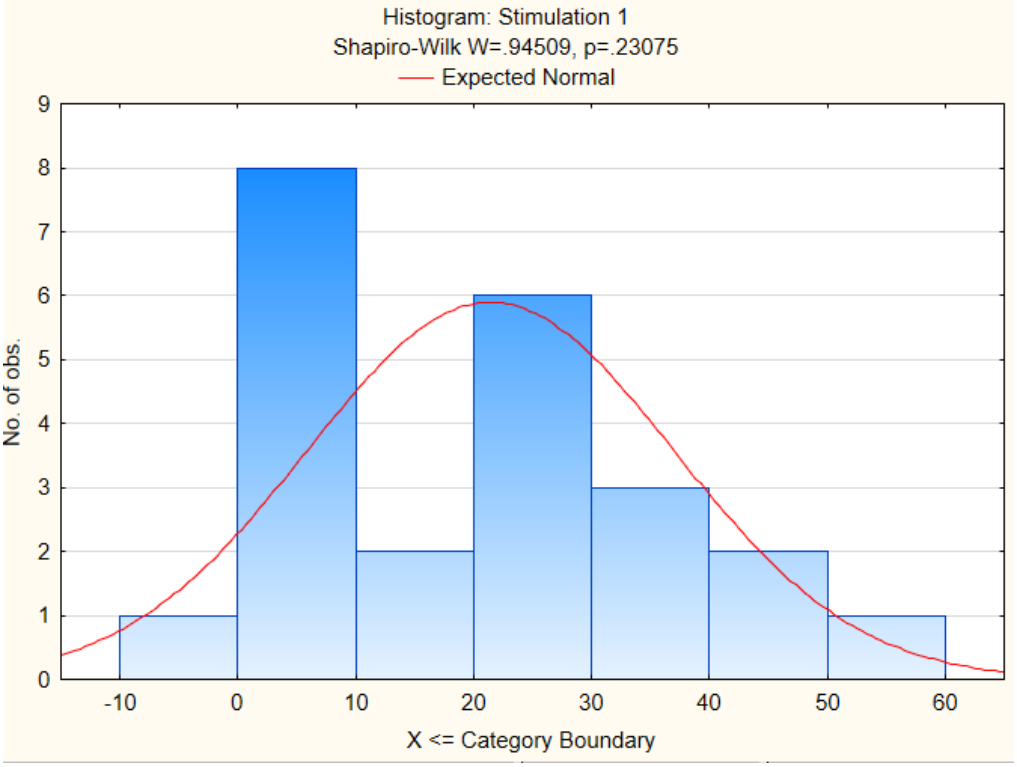


Figure 4.2- ***Graph for the end result of Shapiro-Wilk test for Stimulation 1.****The graph shows thatthe data is not different in from normal and the value of p is 0.23*

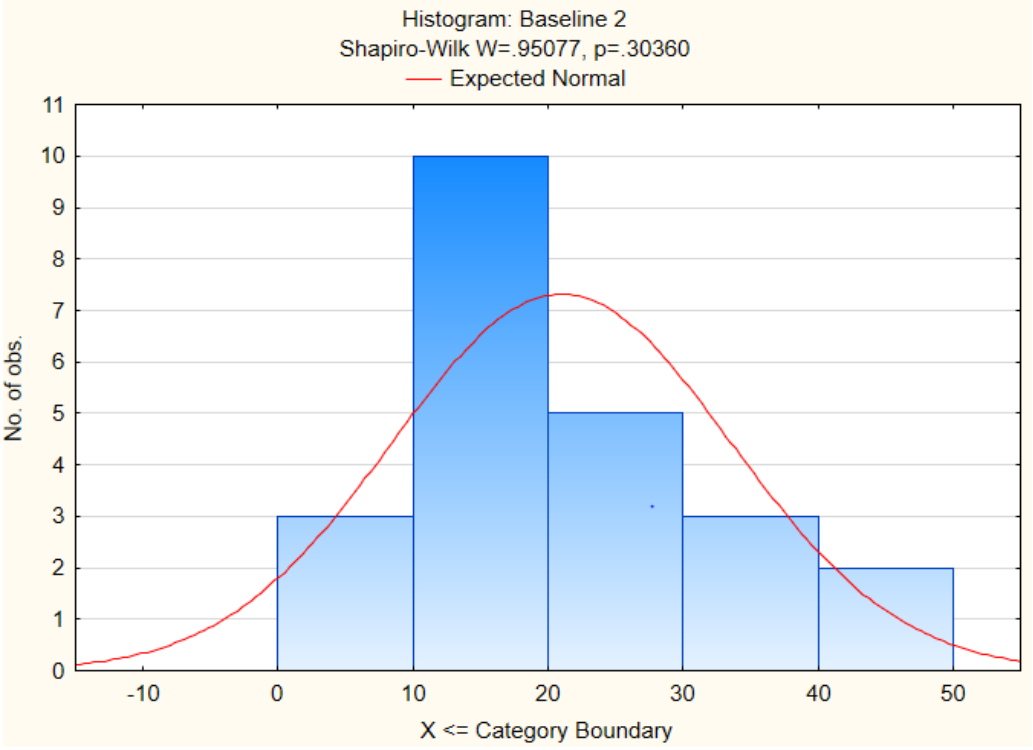


Figure 4.3- ***Graph for the end result of Shapiro-Wilk test for Baseline 2.*** *The graph showsthat the data is not different in from normal and the value of p is 0.303*

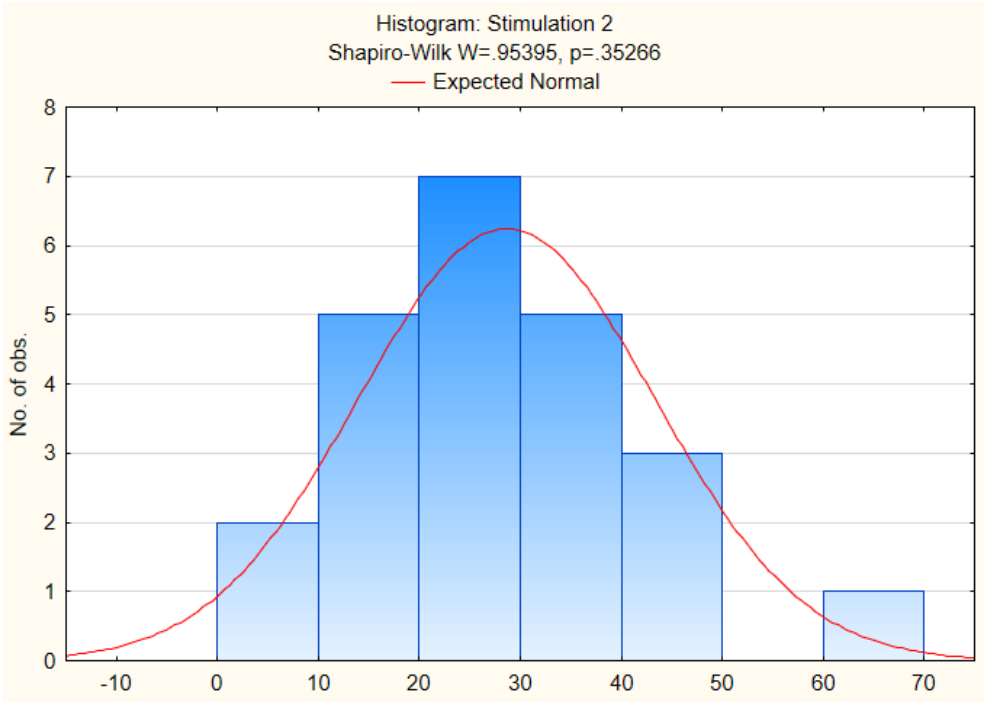


Figure 4.4- ***Graph for the end result of Shapiro-Wilk test for Stimulation 2****. The graph shows thatthe data is not different in from normal and the value of p is 0.352*

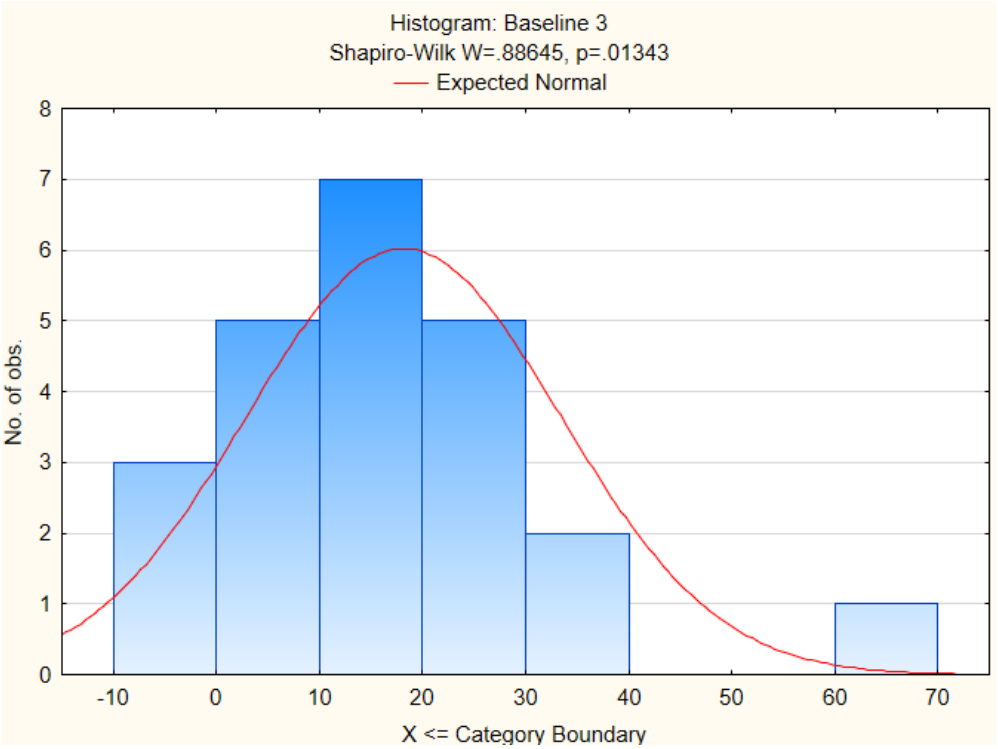


Figure 4.5- ***Graph for the end result of Shapiro-Wilk test for Baseline 3.*** *The graph showsthat the data is not different in from normal and the value of p is 0.581*

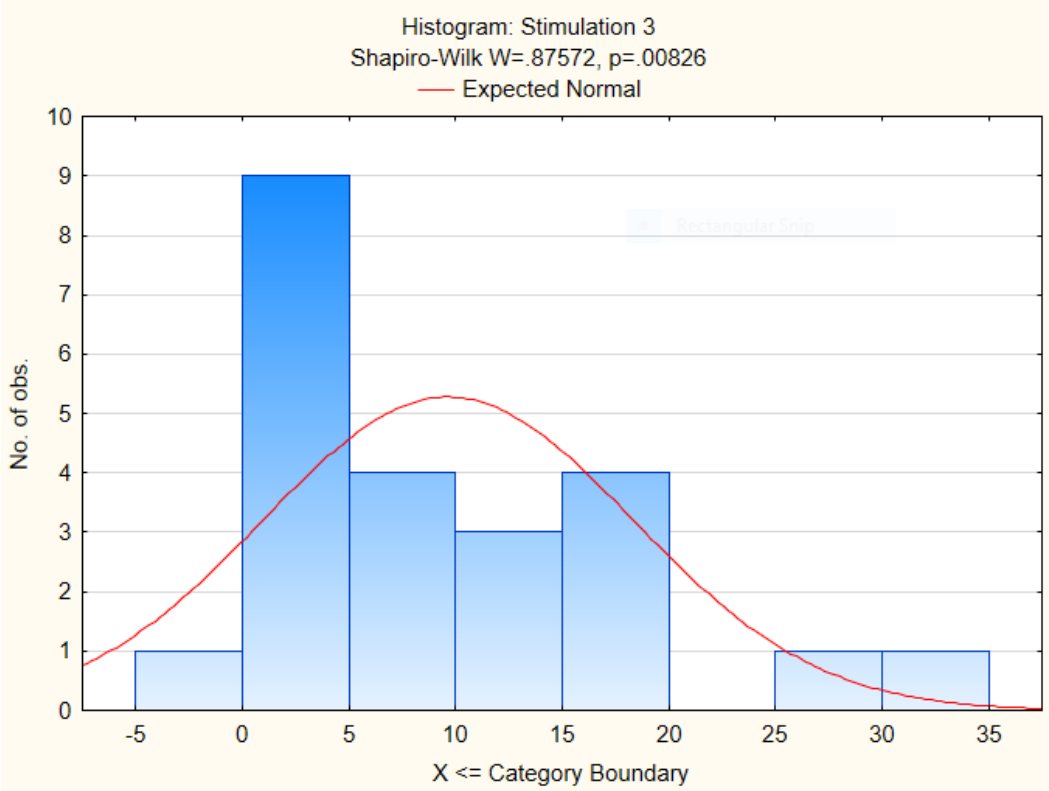


Figure 4.6- ***Graph for the end result of Shapiro-Wilk test for Stimulation 3****. The graph shows that the data is not different in from normal and the value of p is 0.17300*

4.2 Comparison of Baseline of three weeks

The comparison of the three baselines per session was done and illustrated in figure 4.8, and the result within the controls were found to be statistically insignificant ($p>0.05$), indicating that every baseline group has almost near to equal number of correct responses and the means are 19, 21, 18 of Baseline 1, 2 and 3 respectively. Hence, the Figure 4.7 shows that there was no significant difference between them.

Table 4.1- ***Means of correct no. of responses of control***

Cell No.	Control	Mean	Std.Err.	-95.00%	+95.00%	N
	CONTROL; Unweighted Means (Results of 3 stimulations) Current effect: F(2, 44)=.34910, p=.70726 Effective hypothesis decomposition					
1	Baseline 1	19.04348	3.106463	12.60107	25.48589	23
2	Baseline 2	21.00000	2.614191	15.57850	26.42150	23
3	Baseline 3	18.17391	3.177025	11.58517	24.76266	23

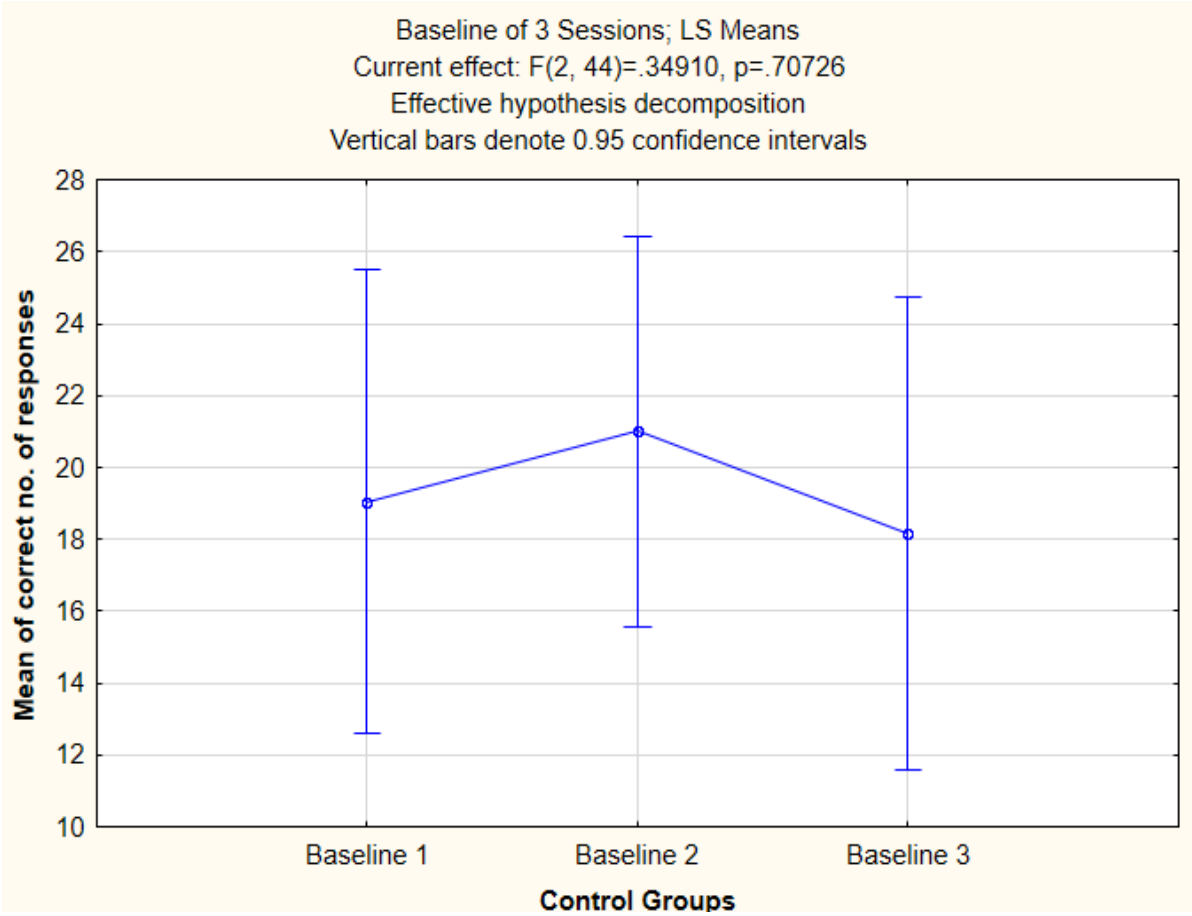


Figure 4.7- ***Repeated measures ANOVA on Control (Baseline 1, Baseline 2 and Baseline 3 are the controls of 3 weeks).****The values in the y-axis represents the mean of correct no. of responses while x-axis represents the control groups of three sessions.Error bars represents Means±SEM.*

4.3 Comparison between Baseline 1 and Sham Stimulation

After administration of one tDCS session (sham), the Baseline 1 was compared with no Stimulation 1, which was Sham stimulation. Figure 4.9 shows the means results of the baseline and stimulation 1 results. The results clearly depicts that there is no statistically significance between the pre-tDCS and Sham tDCS because the value of p is 0.309 which means that it is is greater than 0.05 (Figure4.10). This means that the numbers of correct responses between the Baseline 1 and sham tDCS are not significantly different.

Table 4.2- ***Means of correct no. of responses of pre & with-Sham tDCS***

Cell No.	Sham Session; Unweighted Means (Results of 3 stimulations) Current effect: F(1, 22)=1.0807, p=.30984 Effective hypothesis decomposition					
	Sham	Mean	Std.Err.	-95.00%	+95.00%	N
1	Baseline 1	19.04348	3.106463	12.60107	25.48589	23
2	Stimulation 1	21.43478	3.244226	14.70667	28.16290	23

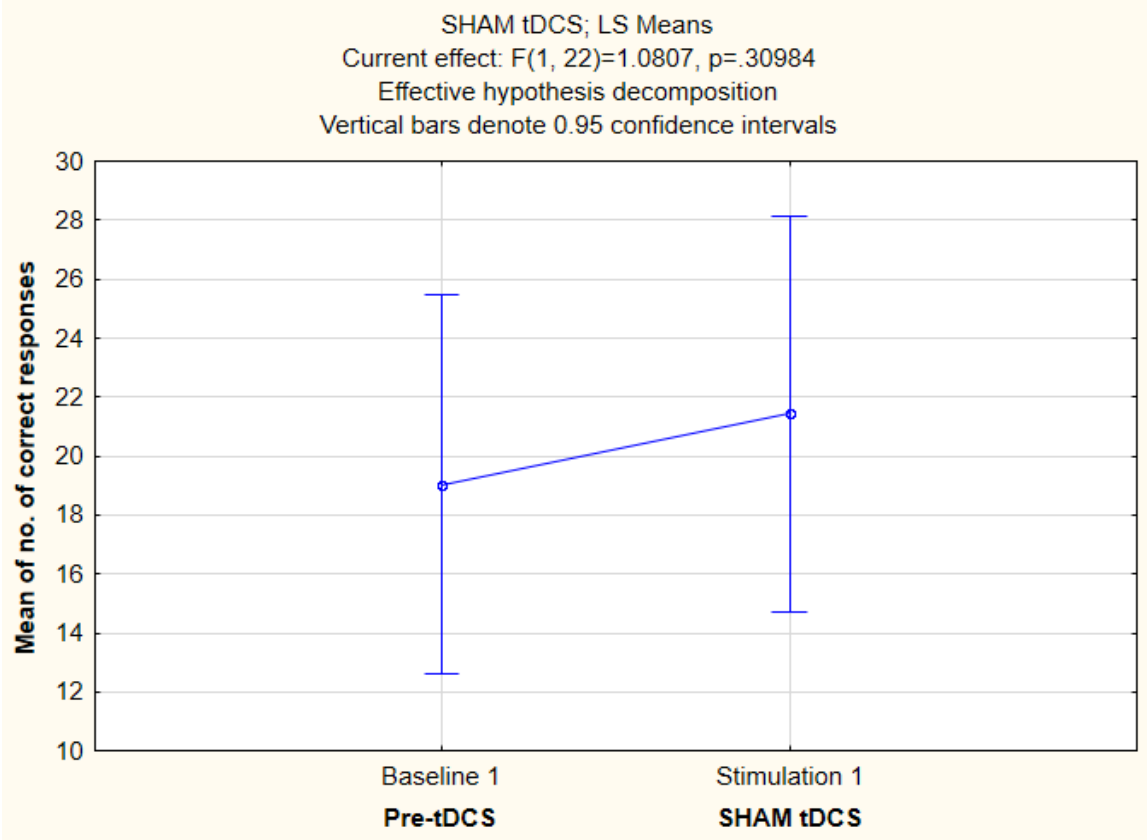


Figure 4.8- ***Repeated measures ANOVA on pre and with Sham tDCS.*** *The difference in the mean no. of correct responses between pre-tDCS and Sham tDCS was not statistically significant (p=0.3098). Error bars represents Means±SEM.*

4.4 Comparison between Baseline 2 and Anodal Stimulation

The Baseline 2 was compared with no Stimulation 2, which was Anodal stimulation. Figure 4.11 shows the means results of the baseline and stimulation 1 results. The results clearly depicts that there is a statistically significance between the pre-tDCS and Sham tDCS because the p value is 0.00001 which is less than 0.05 (Figure 4.12). The result suggests that the numbers of correct responses were increased and illusory effects were decreased.

Table 4.3- ***Means of correct no. of responses of pre & with-Anodal tDCS***

Cell No.	ANODAL; Unweighted Means (Results of 3 stimulations) Current effect: F(1, 22)=32.163, p=.00001 Effective hypothesis decomposition **ANODAL**	DV_1 Mean	DV_1 Std.Err.	DV_1 -95.00%	DV_1 +95.00%	N
1	Baseline 2	21.00000	2.614191	15.57850	26.42150	23
2	Stimulation 2	28.65217	3.064916	22.29593	35.00842	23

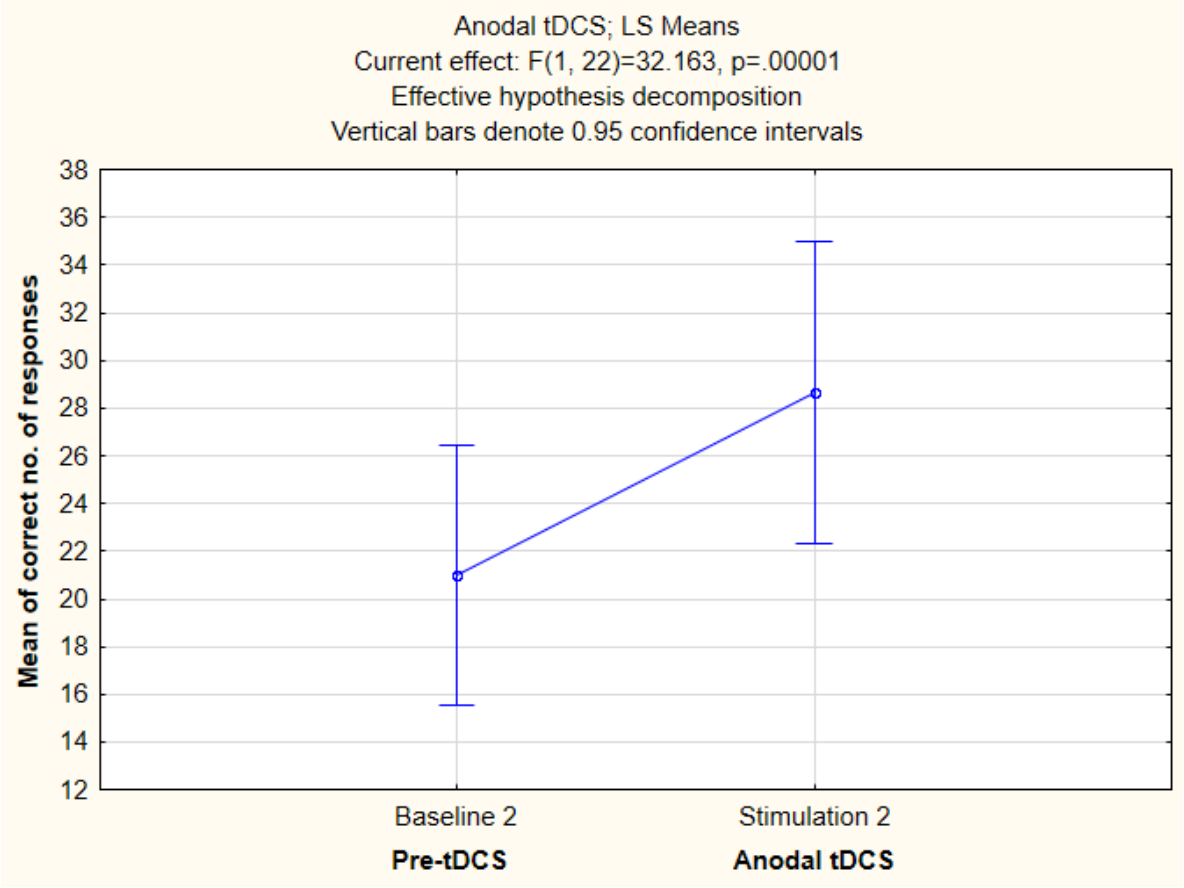


Figure 4.9- ***Comparison of no of correct responses between pre-tDCS and Anodal tDCS session.*** *The difference in the mean no. of correct responses between pre-tDCS and Sham tDCS was statistically significant (p=0.00001). Error bars represents Means±SEM(Repeated measures ANOVA).*

4.5 Comparison between Baseline 3 and Cathodal Stimulation

The Baseline 3 was compared with no Stimulation 3, which was Cathodal stimulation. Figure 4.13 shows the means results of the baseline and stimulation 1 results. The results clearly depicts that there is a statistically significance between the pre-tDCS and Sham tDCS because the value of p is 0.00278 which is less than the value 0.05 (Figure 4.14). The result suggests that the numbers of correct responses were decreased and illusory effects were increased.

Table 4.4- ***Means of correct no. of responses of pre & with-Cathodal tDCS***

Cell No.	CATHODAL; Unweighted Means (Results of 3 stimulations) Current effect: F(1, 22)=11.335, p=.00278 Effective hypothesis decomposition CATHODAL	DV_1 Mean	DV_1 Std.Err.	DV_1 -95.00%	DV_1 +95.00%	N
1	Baseline 3	18.17391	3.177025	11.58517	24.76266	23
2	Stimulation 3	9.65217	1.811916	5.89449	13.40986	23

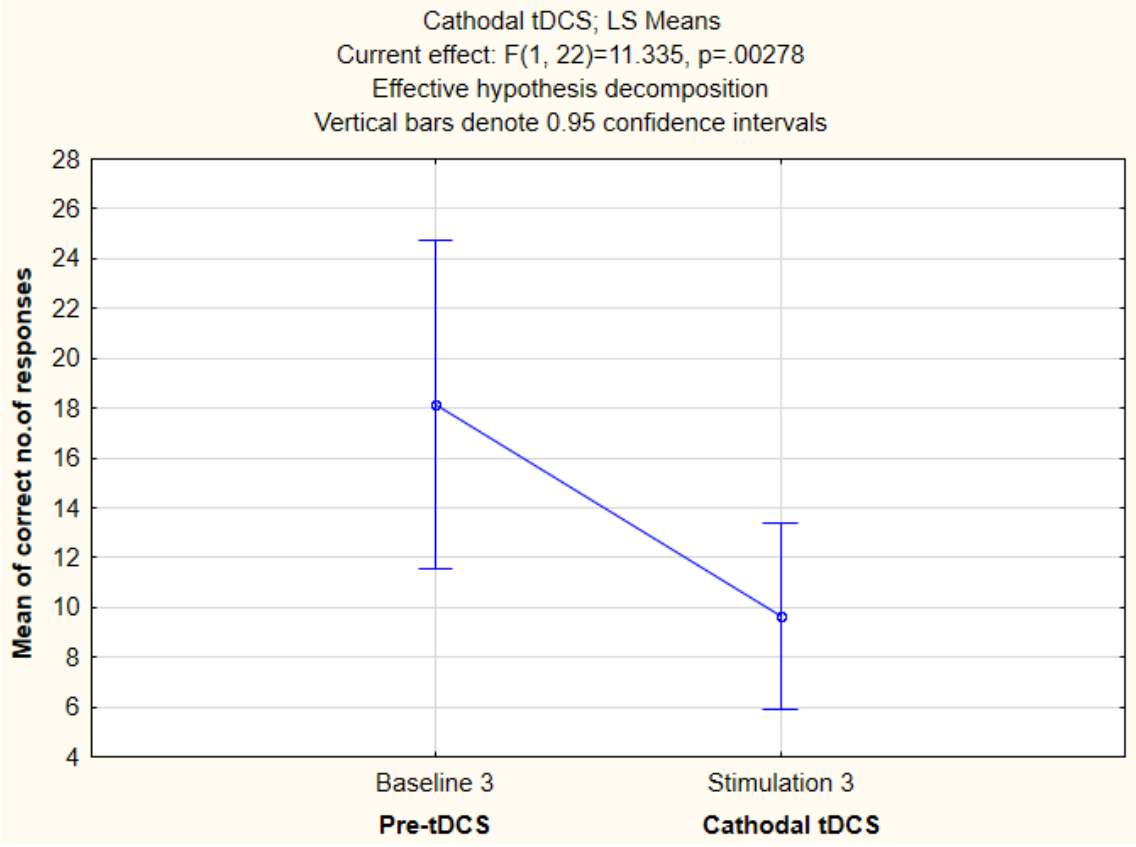


Figure 4.10- ***Comparison of no. of correct responses between pre-tDCS and Anodal tDCS sessions.*** *The difference in the mean no. of correct responses between pre-tDCS and Sham tDCS was statistically significant (p=0.00278). Error bars represents Means±SEM (Repeated measures ANOVA)*

4.6 Cumulative effect of tDCS on Trimodal Integration

Repeated measures ANOVA were conducted to compare the effects of pre and with tDCS interventions. There was a significant outcome of tDCS on the correct number of responses, as the p value is less than 0.05 for the tDCS conditions [F (5,110) = 8.3551, p=0.0000] (Figure.4.13). Following are the means of the pre-tDCS and With-tDCS sessions.

Table 4.5- ***Means of correct no. of responses of all pre & with-tDCS Sessions***

Cell No.	Sessions; Unweighted Means (Results of 3 stimulations) Current effect: F(5, 110)=8.3551, p=.00000 Effective hypothesis decomposition					
	Sessions	Mean	Std.Err.	-95.00%	+95.00%	N
1	Baseline 1	19.04348	3.106463	12.60107	25.48589	23
2	Stimulation 1	21.43478	3.244226	14.70667	28.16290	23
3	Baseline 2	21.00000	2.614191	15.57850	26.42150	23
4	Stimulation 2	28.65217	3.064916	22.29593	35.00842	23
5	Baseline 3	18.17391	3.177025	11.58517	24.76266	23
6	Stimulation 3	9.65217	1.811916	5.89449	13.40986	23

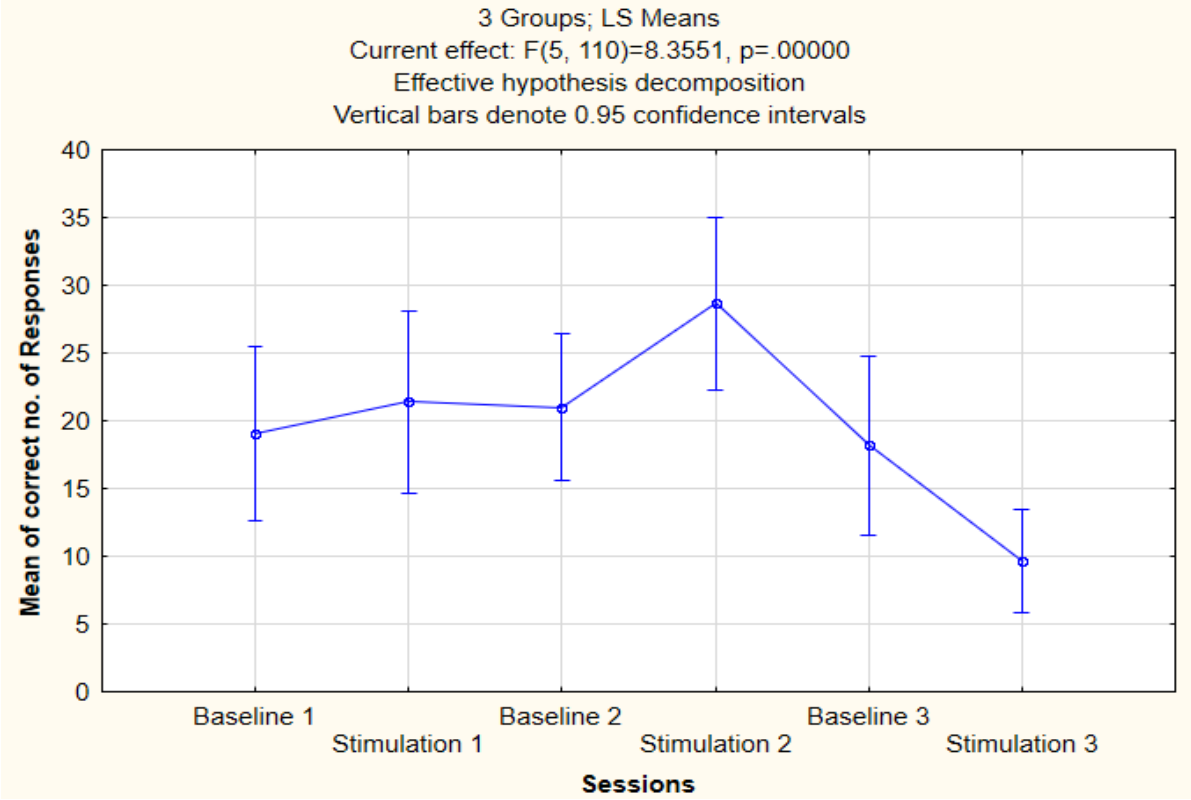


Figure 4.11- ***Comparison of no. of correct responses between pre-tDCS and tDCS of 3 sessions.*** *The difference in the mean no. of correct responses between pre-tDCS and tDCS Interventions was statistically significant (p=0.00000). Error bars represents Means±SEM (Repeated measures ANOVA*

4.7 Post Hoc Analysis

After getting the overall results, Post Hoc comparison using Newman-keul test was used to identify the means which are different from each other, to confirm that where in actual the significant differences occurred between groups. The results indicated that the mean scores of the correct responses control condition were significantly different from Anodal and Cathodal tDCS [F (5,110) =8.3551, p=0.0000].

Table 4.6- ***Post-Hoc comparison using Newman-Keul Test***

Cell No.	Newman-Keuls test; variable DV_1 (Results of 3 Sessions) Approximate Probabilities for Post Hoc Tests Error: Within MS = 103.81, df = 110.00						
	Sessions	{1} 19.043	{2} 21.435	{3} 21.000	{4} 28.652	{5} 18.174	{6} 9.6522
1	Baseline 1		0.706388	0.516397	0.009724	0.772915	0.006483
2	Stimulation 1	0.706388		0.885290	0.018059	0.699264	0.001543
3	Baseline 2	0.516397	0.885290		0.032665	0.615924	0.001550
4	Stimulation 2	0.009724	0.018059	0.032665		0.006296	0.000120
5	Baseline 3	0.772915	0.699264	0.615924	0.006296		0.005550
6	Stimulation 3	0.006483	0.001543	0.001550	0.000120	0.005550	

4.8 Post- tDCS Experiment Experience

Post experiment questionnaire was given to all of the subjects to monitor the side effects of tDCS and it was concluded that none of the subject reported any unbearable effects.

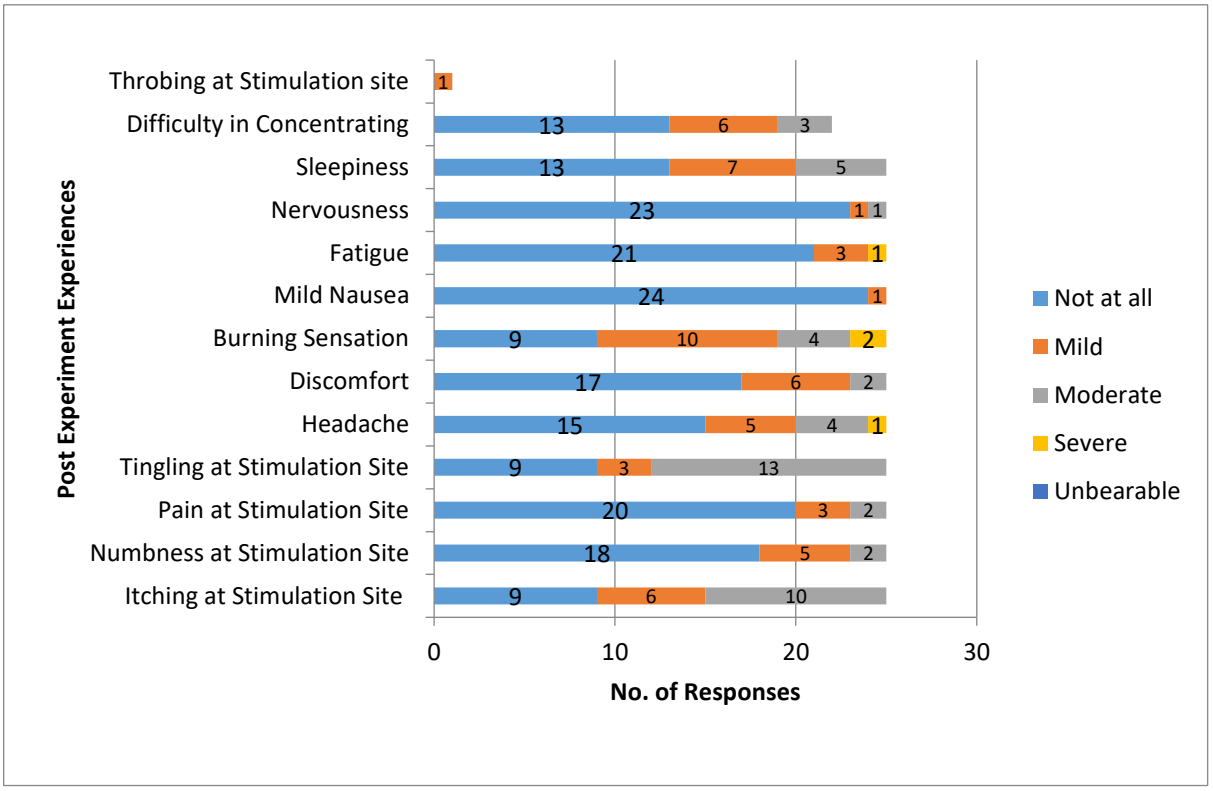


Figure 4.12- ***Post-Experiment Experience of tDCS Sessions***

5 DISCUSSIONS

Transcranial direct current stimulation is an affordable, safe and a cheap procedure which is gaining importance in the fields of research and rehabilitation. The enhancement of human cognitive processes has been a focus of scientific experimentations and tDCS has come to the overcome a lot of diseases and is a potential tool in rehabilitation and in medical research. To date, no significant adverse effects have been reported after the application of tDCS. The maximum effects of tDCS which were reported by the participants were itching, burning sensation, headaches and few had reported that they experience mild nausea.

The present study extends the current knowledge on monitoring the effect of tDCS on multi sensory perception i.e. trimodal integration in healthy humans, showing that the bipolar bilateral montage focusing on right PPC is a key area for neuro-modulation of the sensory information, coming from different senses and merging into the posterior parietal cortex. Thus, this arrangement of montage is a novel technique for application for inhibiting and exciting a brain region and diminishing its contarlateral corresponding part.

5.1 Effect of tDCS on trimodal illusory percept

tDCS can reduce or facilitatevisuo-auditory & tactile interactions and is dependent on the targeted brain regions, polarity of the current, and the illusory percept(Bolognini et al., 2011b). The current study design suggested that the anodal stimulation over P3 depolarizes the neuronal membrane and enhances excitability. Cathodal electrode over P4 hyperpolarizes the neuronal membrane and diminishes P4 excitability, resulting in the increase in illusory effects. Overall, the type of stimulation determines the modulatory effect of tDCS.

5.2 Enhancement of Trimodal integration

In case of perception, every sensory modality is frequently observed independently. On the other hand most objects stimulate different sensory modalities at the same time, thus their integration is crucial (Emiliano Macaluso & Driver, 2005). Similarly, the knowledge of how each specific modality can affect crossmodal perception and how multimodal stimuli are integrated is extremely relevant. This study demonstrates that the bi-parietal tDCS with right anodal posterior parietal cortex improves trimodal integration whereas; left anodal posterior parietal cortex degrades trimodal Integration. Transcranial direct current stimulation has not been widely used for tri-sensory integration although its effect has been observed with respect to the integration of two sensory modalities (Bolognini et al., 2011b). The research has already been done on integration of two modalities i.e, audio-visual, visuo-motor

integration. tDCS targeting PPC is proven to be effective for sensory integration.The PPC exerts both facilitatory and inhibitory effects (Bardi, Kanai, Mapelli, & Walsh, 2013; Santens, Roggeman, Fias, & Verguts, 2010). tDCS over right PPC (rPPC), there was an improvement in visual exploration in audio, visual & audiovisual integration(Mishra, Martínez, & Hillyard, 2010). The results from various researches suggest that tDCS may be a promising means to progress performance of task that entail multisesnosry audio-visual, visuo-spatial and visuomotor integration(Miniussi, Harvey, & Thut, 2015; Costa, Lapenta, Boggio, & Ventura, 2015; Giuseppe Giglia et al., 2015; Klein et al., 2013; C. S. Y. Benwell, Learmonth).

The bi-parietal tDCS has shown that the no. of correct responses were increased, leading to improvement in the task's performance (Bolognini & Maravita, 2011). This means that there is an excitatory as well as inhibitory effect of PPC, depending upon the region of brain being focused. Sensory-specific perceptual conclusions with reference to one sense for example vision, can be noticeably affected by their interaction with additional senses, for example, audition (Bolognini et al., 2010).With respect to our study paradigm, keeping the constant no. of auditory stimuli, audition can affect the interaction of both visual and tactile interactions, leading to illusory percept. Form another study, it was proposed that left PPC is important for disintegration of sensory information keeping reference at contralateral supra orbital region. Hence, the illusory effects were increased as compared to the baseline (Bolognini & Maravita, 2012; Mancini, Bolognini, Bricolo, & Vallar, 2011).

5.3 Effect of bipolar, bilateral balanced tDCS on Sensory processing

Bi-hemispheric bipolar balanced montages can cause an excitatory effect on right PPC and an inhibitory effect on left PPC. Such effects depends upon the stimulation parameters i.e., the polarity of current being administered, the type of evoke multi sensory percept and the stimulated area (C. Benwell, Learmonth, Harvey, & Thut, 2014; Bolognini et al., 2011a; Poreisz et al., 2007). This helping in exciting and area which needs to be boosted and inhibiting the area, where there is a boost in the activity is needed. Conversely, by inhibiting the area which can cause diminishing effect on the area for which the performance needs to be improved (C. S. Y. Benwell et al., 2015; Nikbakht et al., 2018; G. Giglia et al., 2011). This cannot be done while focusing on unipolar montage and keeping another montage as a reference. Thus, bilateral montages may give an insight to monitor the effective neuromodulation of trimodal integration.

5.4 Conclusion

The existing study shows that the bi-parietal right anodal/ left cathodal tDCS can improves the performance of the task, leading to less illusory percept. Conversely,the bi-parietal left anodal & right cathodal tDCS degrades the performance of the task, resulting in an increase in illusory percept. However, this outcome is dependent upon the performance level of the participants in baseline task, in interaction with the administered dosage of tDCS.

Hence, if tDCS is to be enlarged as a research and a clinical means in neurocognitive sciences, it is important to recognize the factors that establish the tDCS outcome across different cognitive fields, and their mutual relationship. By integrating EEG and tDCS concurrently, the actual brain activity can be monitored leading to the more insightful explanation of how the integration and disintegration of the sensory information occurs.

5.5 Limitations

The present study has following are the limitations;

- Hardware for tactile stimulation should be fabricated such as to get the accurate and precise timings.
- The software application used to generate and synchronize the stimulations is a bottle neck in our study and have high impact on synchronization due to involvement of multiple resources allocation and deallocation repeatedly.

5.6 Future Consideration

From our results, transcranial direct current stimulation on right posterior parietal cortex may have an excitatory effect on the targeted neuronal cells. The correct number of responses was recorded manually & there might exist the chance of incorrect recording of responses. There is a possibility that after every trial, the correct number of responses may also be recorder by using the same software and the subject can effectively click any of the option from those displayed on the screen. By integrating EEG and tDCS concurrently, the actual brain activity can be monitored leading to the more insightful explanation of how the integration and disintegration of the sensory information occurs.

Whereas, the left posterior parietal cortex have an inhibitory effect. However, we only observed the correct no. of scores of the participants and not the physiological changes being produced by this stimulation. Many studies related to tDCS were found to make functional improvement in the neuronal activity of the targeted region.

There is a hope to develop a protocol which can analyze tDCS and task performance with any brain function monitoring technique like EEG activity with and improves the neurocognitive dysfunction (Autism, Sensory Integration Dysfunction, Sensory based motor Disorder, Sensory Discrimination Disorder, Sensory Modulation Disorder). These findings may be useful for studies about the therapeutic mechanism of tDCS.

APPENDIX A

A Testing of timings of the 3 modalities:

The comparative timing of stimuli was amended in a manner that the middle sequence of stimuli in every modality was associated with the middle sequence of other modalities. The accuracy of timing was checked with the Power Lab hardware and Lab Chart software. 3 BNC connectors as well as three oscilloscopes' wires were used.

A.1 Flash

For testing of flash, oscilloscope wire was connected to the BNC connector on channel no.1 and earphones were used. Figure 3.8 illustrates a small circuitry was made using Phototransistor ST-1KL3B and a comparator LM324Ic (Op-amp). The ground was connected with ground clip of oscilloscope whereas the probe is connected to the positive/output terminal of the circuit. 3.4 V is given via power supply.

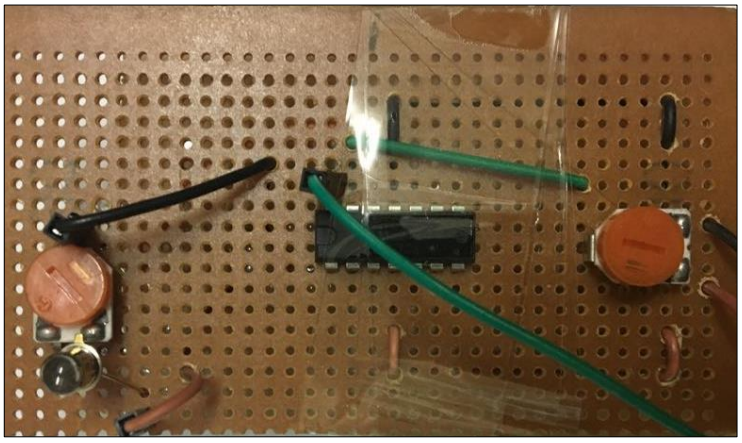


Figure A 1- ***PCB circuit for testing of flashes.***

A.2 Beep

For testing beep, channel 2 of Power lab, oscilloscope wire and earphones were used. Left or right earphone was cut; the ground of it was checked by using digital multimeter. The ground clip of oscilloscope was connected with ground of the earphone, whereas the probe was connected to the output of the earphone.

A.3 Tap

For testing tap, channel 3 of Power lab, IR encoder H2010 and earphones were used. The IR encoder was attached on an adjustable lab stand, ground and output was connected to the ground clip and probe respectively. The Voltage applied was 44V (via 2 power supplies).

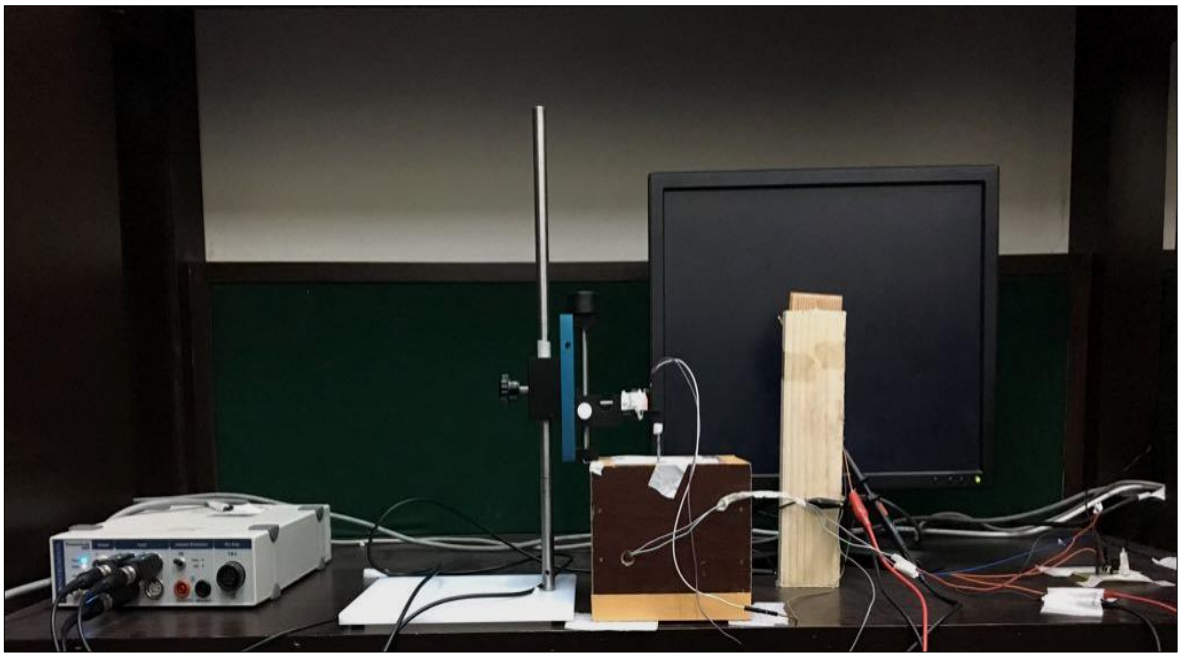


Figure A 2- ***Testing of the three modalities (beeps, taps and flashes) with the help of Power lab.***

A.4 Powerlab Output of the channels on Lab Chart 8

The sampling rate was 100 kHz and the trials were run for 100 times for each condition for a total of 600 trials .The first Channel shown in red in showing the testing of Flashes, the Second in blue is showing the testing of Beeps and the third Channel in green is displaying the output of the tap. The distance between the two consecutive taps, beeps and flashes is inter-tap, inter-beep and inter-flash respectively. Inter-beep, inter-tap and inter-flash duration is 65miliseconds which is equivalent to five refresh rates of the monitor. The duration of the flash, beep and tap was 13 milliseconds which was equivalent to one refresh rate.

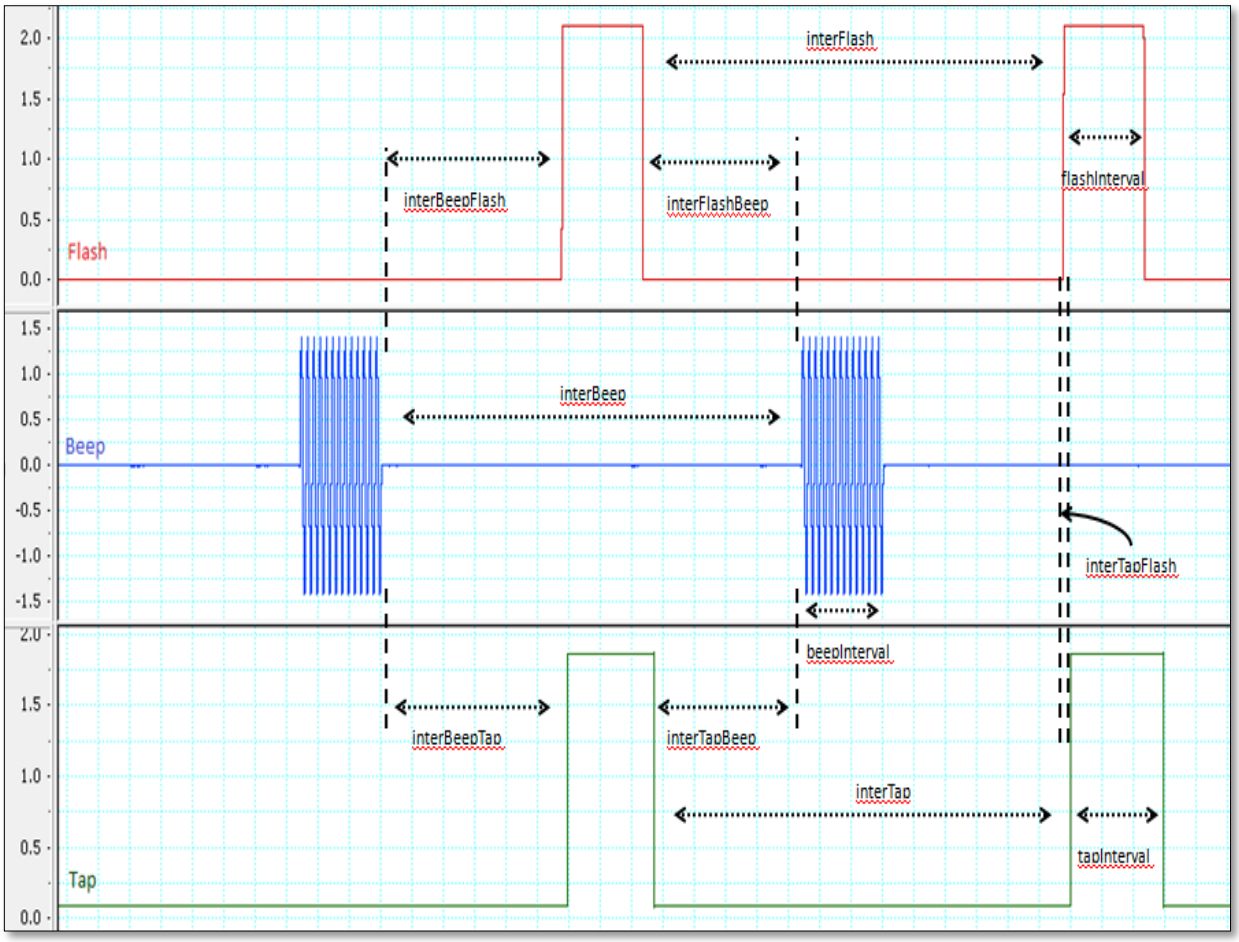


Figure A 3- ***Power lab output of the channels on Lab Chart 8. x-axis represents time and y-axis represent voltage.***

References

Akrami, A., Kopec, C. D., Diamond, M. E., & Brody, C. D. (2018). Posterior parietal cortex represents sensory history and mediates its effects on behaviour. *Nature*. https://doi.org/10.1038/nature25510

Bardi, L., Kanai, R., Mapelli, D., & Walsh, V. (2013). Direct current stimulation (tDCS) reveals parietal asymmetry in local/global and salience-based selection. *Cortex*. https://doi.org/10.1016/j.cortex.2012.04.016

Battaglia, P. W., Jacobs, R. A., & Aslin, R. N. (2003). Bayesian integration of visual and auditory signals for spatial localization. *Journal of the Optical Society of America A*. https://doi.org/10.1364/JOSAA.20.001391

Bear, M. F., & Malenka, R. C. (1994). Synaptic plasticity: LTP and LTD. *Current Opinion in Neurobiology*. https://doi.org/10.1016/0959-4388(94)90101-5

Benwell, C., Learmonth, G., Harvey, M., & Thut, G. (2014). The effects of bilateral transcranial direct current stimulation over posterior parietal cortices on visuospatial attention bias. *Clinical Neurophysiology*.

Benwell, C. S. Y., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*, *69*, 152–165. https://doi.org/10.1016/j.cortex.2015.05.007

Berryhill, M. E. (2014). Hits and misses: leveraging tDCS to advance cognitive research. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2014.00800

Bhattacharya, J., Shams, L., & Shimojo, S. (2002). Sound-induced illusory flash perception: Role of gamma band responses. *NeuroReport*. https://doi.org/10.1097/00001756-200210070-00007

Bikson, M., Datta, A., Rahman, A., & Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: Role of " return" electrode's position and size. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2010.05.020

Bikson, M., Parra, L., Datta, A., Dmochowski, J., Minhas, P., Truong, D., … Rahman, A. (n.d.). Targeting of transcranial Direct Current Stimulation (tDCS) Transcranial Direct Current Stimulation (tDCS).

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology*, *11*(2), 249–254. https://doi.org/10.1017/S1461145707007833

Bolognini, N., Fregni, F., Casati, C., Olgiati, E., & Vallar, G. (2010). Brain polarization of parietal cortex augments training-induced improvement of visual exploratory and attentional skills. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.06.053

Bolognini, N., & Maravita, A. (2011). Uncovering multisensory processing through non-invasive brain stimulation. *Frontiers in Psychology*, *2*(MAR), 1–10. https://doi.org/10.3389/fpsyg.2011.00046

Bolognini, N., & Maravita, A. (2012). Interactions between senses: Updating on neural mechanisms and behavioral evidence. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2012.00122

Bolognini, N., Rossetti, A., Casati, C., Mancini, F., & Vallar, G. (2011a). Neuromodulation of multisensory perception: A tDCS study of the sound-induced flash illusion. *Neuropsychologia*, *49*(2), 231–237. https://doi.org/10.1016/j.neuropsychologia.2010.11.015

Bolognini, N., Rossetti, A., Casati, C., Mancini, F., & Vallar, G. (2011b). Neuromodulation of multisensory perception: A tDCS study of the sound-induced flash illusion. *Neuropsychologia*, *49*(2), 231–237. https://doi.org/10.1016/j.neuropsychologia.2010.11.015

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*,*14*(8), 1133–1145.

https://doi.org/10.1017/S1461145710001690

Brunoni, A. R., Boggio, P. S., Ferrucci, R., Priori, A., & Fregni, F. (2013). Transcranial direct current stimulation: challenges, opportunities, and impact on psychiatry and neurorehabilitation. *Frontiers in Psychiatry*, *4*, 19. https://doi.org/10.3389/fpsyt.2013.00019

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., … Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation*, *5*(3), 175–195. https://doi.org/10.1016/j.brs.2011.03.002

Cabral, M. E., Baltar, A., Borba, R., Galvão, S., Santos, L., Fregni, F., & Monte-Silva, K. (2015). Transcranial direct current stimulation. *NeuroReport*. https://doi.org/10.1097/WNR.0000000000000397

Calvert, G. a. (2001). Crossmodal processing in the human brain: Insights from functional neuroimaging studies, 1110–1123. https://doi.org/10.1093/cercor/11.12.1110

Calvert, G., Campbell, R., & Brammer, M. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Current Biology*. https://doi.org/10.1016/S0960-9822(00)00513-3

Calvert, G., Spence, C., & Stein, B. E. (2004). The handbook of multisensory processes. *The Handbook of Multisensory Processes*. https://doi.org/nicht verfügbar?

Chrysikou, E. G., Mary Greene, C., Beaty, R., Rosen, D. S., Erickson, B., Kim, Y. E., … Kounios, J. (2016). ROSEN (2016) ANODAL tDCS. *Article Front. Hum. Neurosci*. https://doi.org/10.3389/fnhum.2016.00579

Costa, T. L., Lapenta, O. M., Boggio, P. S., & Ventura, D. F. (2015). Transcranial direct current stimulation as a tool in the study of sensory-perceptual processing. *Attention, Perception, and Psychophysics*, *77*(6), 1813–1840. https://doi.org/10.3758/s13414-015-0932-3

Dissanayaka, T. D., Zoghi, M., Farrell, M., Egan, G. F., & Jaberzadeh, S. (2018). Sham transcranial electrical stimulation and its effects on corticospinal excitability: a

systematic review and meta-analysis. *Reviews in the Neurosciences*, *29*(2), 223–232. https://doi.org/10.1515/revneuro-2017-0026

Driver, J., & Noesselt, T. (2008). Multisensory Interplay Reveals Crossmodal Influences on "Sensory-Specific" Brain Regions, Neural Responses, and Judgments. *Neuron*. https://doi.org/10.1016/j.neuron.2007.12.013

Ernst, M. O. (2005). The "puzzle" of sensory perception: Putting together multisensory information. In *Proceedings of the Seventh International Conference on Multimodal Interfaces, ICMI'05*. https://doi.org/10.1145/1088463.1088464

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature*. https://doi.org/10.1038/415429a

Fertonani, A., & Miniussi, C. (2017). Transcranial electrical stimulation: What we know and do not know about mechanisms. *Neuroscientist*, *23*(2), 109–123. https://doi.org/10.1177/1073858416631966

Fetsch, C. R., Deangelis, G. C., & Angelaki, D. E. (2013). Bridging the gap between theories of sensory cue integration and the physiology of multisensory neurons. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3503

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends Neurosci*, *37*(12), 742–753. https://doi.org/10.1016/j.tins.2014.08.003

Foxe, J. J., Morocz, I. A., Murray, M. M., Higgins, B. A., Javitt, D. C., & Schroeder, C. E. (2000). Multisensory auditory-somatosensory interactions in early cortical processing revealed by high-density electrical mapping. *Cognitive Brain Research*. https://doi.org/10.1016/S0926-6410(00)00024-0

Giard, M. H., & Peronnet, F. (1999). Auditory-Visual Integration during Multimodal Object Recognition in Humans: A Behavioral and Electrophysiological Study. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/089892999563544

Giglia, G., Mattaliano, P., Puma, A., Rizzo, S., Fierro, B., & Brighina, F. (2011). Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects.

Brain Stimulation. https://doi.org/10.1016/j.brs.2011.01.003

Giglia, G., Pia, L., Folegatti, A., Puma, A., Fierro, B., Cosentino, G., … Brighina, F. (2015). Far space remapping by tool use: A rTMS study over the right posterior parietal cortex. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2015.01.412

Goetz, S. M., & Peterchev, A. V. (2012). A model of variability in brain stimulation evoked responses. In *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*. https://doi.org/10.1109/EMBC.2012.6347467

Grimaldi, G., Argyropoulos, G. P., Bastian, A., Cortes, M., Davis, N. J., Edwards, D. J., … Celnik, P. (2016). Cerebellar Transcranial Direct Current Stimulation (ctDCS): A Novel Approach to Understanding Cerebellar Function in Health and Disease. *Neuroscientist*, *22*(1), 83–97. https://doi.org/10.1177/1073858414559409

Hötting, K., & Röder, B. (2004). Hearing Cheats Touch, but Less in Congenitally Blind Than in Sighted Individuals. *Psychological Science*. https://doi.org/10.1111/j.0963-7214.2004.01501010.x

King, A. J., & Calvert, G. A. (2001). Multisensory integration: Perceptual grouping by eye and ear. *Current Biology*, *11*(8), 322–325. https://doi.org/10.1016/S0960-9822(01)00175-0

Klein, E., Mann, A., Huber, S., Bloechle, J., Willmes, K., Karim, A. A., … Moeller, K. (2013). Bilateral Bi-Cephalic Tdcs with Two Active Electrodes of the Same Polarity Modulates Bilateral Cognitive Processes Differentially. *PLoS ONE*, *8*(8), 1–11. https://doi.org/10.1371/journal.pone.0071607

Krause, B., & Cohen Kadosh, R. (2013). Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. *Developmental Cognitive Neuroscience*, *6*, 176–194. https://doi.org/10.1016/j.dcn.2013.04.001

Kronberg, G., Bridi, M., Abel, T., Bikson, M., & Parra, L. C. (2017). Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2016.10.001

Kumru, H., Soler, D., Vidal, J., Navarro, X., Tormos, J. M., Pascual-Leone, a, & Valls-Sole, J. (2013). The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: an evoked potentials and quantitative thermal testing study. *European Journal of Pain (London, England)*. https://doi.org/10.1002/j.1532-2149.2012.00167.x

Lacey, S., & Sathian, K. (2015). CROSSMODAL AND MULTISENSORY INTERACTIONS BETWEEN VISION AND TOUCH. *Scholarpedia Journal*, *10*(3), 7957. https://doi.org/10.4249/scholarpedia.7957

Lange, J., Oostenveld, R., & Fries, P. (2011). Perception of the touch-induced visual double-flash illusion correlates with changes of rhythmic neuronal activity in human visual and somatosensory areas. *NeuroImage*, *54*(2), 1395–1405. https://doi.org/10.1016/j.neuroimage.2010.09.031

Lefebvre, S., Laloux, P., Peeters, A., Desfontaines, P., Jamart, J., & Vandermeeren, Y. (2013). Dual-tDCS Enhances Online Motor Skill Learning and Long-Term Retention in Chronic Stroke Patients. *Frontiers in Human Neuroscience*, *6*(January), 1–17. https://doi.org/10.3389/fnhum.2012.00343

Lewis, J. W., Beauchamp, M. S., & DeYoe, E. A. (2000). A comparison of visual and auditory motion processing in human cerebral cortex. *Cerebral Cortex*. https://doi.org/10.1093/cercor/10.9.873

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in Cellular Neuroscience*. https://doi.org/10.3389/fncel.2015.00181

Liebetanz, D. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*(10), 2238–2247. https://doi.org/10.1093/brain/awf238

Lindenberg, R., Renga, V., Zhu, L. L., Nair, D., & Schlaug, G. (2010). Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology*. https://doi.org/10.1212/WNL.0b013e318202013a

Macaluso, E., & Driver, J. (2005). Multisensory spatial interactions: A window onto

functional integration in the human brain. *Trends in Neurosciences*, *28*(5), 264–271. https://doi.org/10.1016/j.tins.2005.03.008

Macaluso, E., Frith, C. D., & Driver, J. (2001). Multimodal mechanisms of attention related to rates of spatial shifting in vision and touch. *Experimental Brain Research*. https://doi.org/10.1007/s002210000656

Mancini, F., Bolognini, N., Bricolo, E., & Vallar, G. (2011). Cross-modal processing in the occipito-temporal cortex: a TMS study of the Müller-Lyer illusion. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21561

Marques, L. M., Lapenta, O. M., Merabet, L. B., Bolognini, N., & Boggio, P. S. (2014). Tuning and disrupting the brainâ€"modulating the McGurk illusion with electrical stimulation. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2014.00533

Martin, D. M., Liu, R., Alonzo, A., Green, M., & Loo, C. K. (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Experimental Brain Research*, *232*(10), 3345–3351. https://doi.org/10.1007/s00221-014-4022-x

Mishra, J., Martínez, A., & Hillyard, S. A. (2010). Effect of Attention on Early Cortical Processes Associated with the Sound-induced Extra Flash Illusion. *Journal of Cognitive Neuroscience*, *22*(8), 1714–1729. https://doi.org/10.1162/jocn.2009.21295

Mohammadi, A. (2016). Induction of Neuroplasticity by Transcranial Direct Current Stimulation. *J Biomed Phys Eng.*, *6*(4), 205–208. https://doi.org/10.1016/S0379-7112(97)82714-2

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., & Priori, A. (2013). Transcranial direct current stimulation (tDCS) and language. *Journal of Neurology, Neurosurgery and Psychiatry*, *84*(8), 832–842. https://doi.org/10.1136/jnnp-2012-302825

Mulkey, R., Herron, C., & Malenka, R. (1993). An essential role for protein phosphatases in hippocampal long-term depression. *Science*, *261*(5124), 1051–1055. https://doi.org/10.1126/science.8394601

Nasseri, P., Nitsche, M. A., & Ekhtiari, H. (2015). A framework for categorizing electrode montages in transcranial direct current stimulation. *Frontiers in Human Neuroscience*, *9*(February), 1–5. https://doi.org/10.3389/fnhum.2015.00054

Nava, E., Grassi, M., & Turati, C. (2016). Audio-visual, visuo-tactile and audio-tactile correspondences in preschoolers. *Multisensory Research*, *29*(1–3), 93–111. https://doi.org/10.1163/22134808-00002493

Niedermeyer, E., & Lopes da Silva, F. H. (2005). *Electroencephalography : basic principles, clinical applications, and related fields*. Lippincott Williams & Wilkins.

Nikbakht, N., Tafreshiha, A., Zoccolan, D., & Diamond, M. E. (2018). Supralinear and Supramodal Integration of Visual and Tactile Signals in Rats: Psychophysics and Neuronal Mechanisms. *Neuron*. https://doi.org/10.1016/j.neuron.2018.01.003

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., … Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/j.brs.2008.06.004

Nitsche, M. A., Niehaus, L., Hoffmann, K. T., Hengst, S., Liebetanz, D., Paulus, W., & Meyer, B. U. (2004). MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. *Clin Neurophysiol*. https://doi.org/10.1016/j.clinph.2004.05.001

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., & Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology*, *114*(4), 600–604. https://doi.org/10.1016/S1388-2457(02)00412-1

Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S., … Tergau, F. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of Physiology*, *568*(1), 291–303. https://doi.org/10.1113/jphysiol.2005.092429

Nitsche, M., Antal, A., Liebetanz, D., & Lang, N. (2007). … and Modulation of Neuroplasticity by Transcranial Direct Current Stimulation. *Transcranial Brain …*.

Paulus, W. (2003a). Transcranial direct current stimulation ({tDCS)}. *Supplements to Clinical Neurophysiology*. https://doi.org/10.1016/S1567-424X(09)70229-6

Paulus, W. (2003b). Transcranial direct current stimulation (tDCS). *Suppl Clin Neurophysiol*. https://doi.org/10.1016/S1567-424X(09)70229-6

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*(4–6), 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004

Qin, W., & Yu, C. (2013). Neural pathways conveying novisual information to the visual cortex. *Neural Plasticity*. https://doi.org/10.1155/2013/864920

Quiroga, R. Q., Reddy, L., Kreiman, G., Koch, C., & Fried, I. (2005). Invariant visual representation by single neurons in the human brain. *Nature*. https://doi.org/10.1038/nature03687

Raij, T., Uutela, K., & Hari, R. (2000). Audiovisual integration of letters in the human brain. *Neuron*. https://doi.org/10.1016/S0896-6273(00)00138-0

Ricciardi, E., Basso, D., Sani, L., Bonino, D., Vecchi, T., Pietrini, P., & Miniussi, C. (2011). Functional inhibition of the human middle temporal cortex affects non-visual motion perception: A repetitive transcranial magnetic stimulation study during tactile speed discrimination. *Experimental Biology and Medicine*. https://doi.org/10.1258/ebm.2010.010230

Ricciardi, E., Vanello, N., Sani, L., Gentili, C., Scilingo, E. P., Landini, L., … Pietrini, P. (2007). The effect of visual experience on the development of functional architecture in hMT+. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhm018

Riggall, K., Forlini, C., Carter, A., Hall, W., Weier, M., Partridge, B., & Meinzer, M. (2015). Researchers' perspectives on scientific and ethical issues with transcranial direct current stimulation: An international survey. *Scientific Reports*. https://doi.org/10.1038/srep10618

Rizzolatti, G., & Matelli, M. (2003). Two different streams form the dorsal visual system: Anatomy and functions. In *Experimental Brain Research*.

https://doi.org/10.1007/s00221-003-1588-0

Rockland, K. S., & Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. In *International Journal of Psychophysiology*. https://doi.org/10.1016/S0167-8760(03)00121-1

Romero Lauro, L. J., Rosanova, M., Mattavelli, G., Convento, S., Pisoni, A., Opitz, A., … Vallar, G. (2014). TDCS increases cortical excitability: direct evidence from TMS-EEG. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *58*, 99–111. https://doi.org/10.1016/j.cortex.2014.05.003

Roy, D., Steyer, G. J., Gargesha, M., Stone, M. E., & Wilson, L. (2009). NIH Public Access, *292*(3), 342–351. https://doi.org/10.1002/ar.20849.3D

Ruffini, G., & Barcelona, N. S. (2013). tDCS clinical research -highlights: Cognitive Enhancement Neuroelectrics White Paper WP201305.

Santens, S., Roggeman, C., Fias, W., & Verguts, T. (2010). Number processing pathways in human parietal cortex. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhp080

Schestatsky, P., Morales-Quezada, L., & Fregni, F. (2013). Simultaneous EEG Monitoring During Transcranial Direct Current Stimulation. *Journal of Visualized Experiments*, (76), 1–11. https://doi.org/10.3791/50426

Shams, L., Iwaki, S., Chawla, A., & Bhattacharya, J. (2005). Early modulation of visual cortex by sound: An MEG study. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2004.12.035

Shams, L., Kamitani, Y., & Shimojo, S. (2002). Visual illusion induced by sound. *Cognitive Brain Research*, *14*(1), 147–152. https://doi.org/10.1016/S0926-6410(02)00069-1

Shams, L., Kamitani, Y., Thompson, S., & Shimojo, S. (2001). Sound alters visual evoked potentials in humans. *NeuroReport*. https://doi.org/10.1097/00001756-200112040-00049

Shams, L., Ma, W. J., & Beierholm, U. (2005). Sound-induced flash illusion as an optimal percept. *NeuroReport*, *16*(17), 1923–1927. https://doi.org/10.1097/01.wnr.0000187634.68504.bb

Shimojo, S., & Shams, L. (2001). Sensory modalities are not separate modalities: Plasticity and interactions. *Current Opinion in Neurobiology*, *11*(4), 505–509. https://doi.org/10.1016/S0959-4388(00)00241-5

Siciliano, R., Hirata, Y., & Kelly, S. D. (2016). Electrical Stimulation Over Left Inferior Frontal Gyrus Disrupts Hand Gesture's Role in Foreign Vocabulary Learning. *Educational Neuroscience*, *1*, 237761611665240. https://doi.org/10.1177/2377616116652402

Stagg, C. J., & Nitsche, M. A. (2011a). Physiological basis of transcranial direct current stimulation. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*. https://doi.org/10.1177/1073858410386614

Stagg, C. J., & Nitsche, M. A. (2011b). Physiological Basis of Transcranial Direct Current Stimulation. *The Neuroscientist*. https://doi.org/10.1177/1073858410386614

Tadini, L., El-Nazer, R., Brunoni, A. R., Williams, J., Carvas, M., Boggio, P., … Fregni, F. (2011). Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. *Journal of ECT*. https://doi.org/10.1097/YCT.0b013e3181e631a8

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial direct current stimulation (tDCS): A Beginner's guide for design and implementation. *Frontiers in Neuroscience*, *11*(NOV), 641. https://doi.org/10.3389/fnins.2017.00641

van Dun, K., Bodranghien, F. C. A. A., Mariën, P., & Manto, M. U. (2016a). tDCS of the Cerebellum: Where Do We Stand in 2016? Technical Issues and Critical Review of the Literature. *Frontiers in Human Neuroscience*, *10*(May). https://doi.org/10.3389/fnhum.2016.00199

van Dun, K., Bodranghien, F. C. A. A., Mariën, P., & Manto, M. U. (2016b). tDCS of the Cerebellum: Where Do We Stand in 2016? Technical Issues and Critical Review of the Literature. *Frontiers in Human Neuroscience*, *10*, 199. https://doi.org/10.3389/fnhum.2016.00199

Vannorsdall, T. D., Van Steenburgh, J. J., Schretlen, D. J., Jayatillake, R., Skolasky, R. L., & Gordon, B. (2016). Reproducibility of tDCS results in a randomized trial: Failure to

replicate findings of tDCS-induced enhancement of verbal fluency. *Cognitive and Behavioral Neurology*, *29*(1), 11–17. https://doi.org/10.1097/WNN.0000000000000086

Vaseghi, B., Zoghi, M., & Jaberzadeh, S. (2015). Differential effects of cathodal transcranial direct current stimulation of prefrontal, motor and somatosensory cortices on cortical excitability and pain perception - a double-blind randomised sham-controlled study. *European Journal of Neuroscience*, *42*(7), 2426–2437. https://doi.org/10.1111/ejn.13043

Violentyev, A., Shimojo, S., & Shams, L. (2005). Touch-induced visual illusion. *NeuroReport*, *16*(10), 1107–1110. https://doi.org/10.1097/00001756-200507130-00015

Watkins, S., Shams, L., Tanaka, S., Haynes, J. D., & Rees, G. (2006). Sound alters activity in human V1 in association with illusory visual perception. *NeuroImage*, *31*(3), 1247–1256. https://doi.org/10.1016/j.neuroimage.2006.01.016

Weiss, P. H., Achilles, E. I. S., Moos, K., Hesse, M. D., Sparing, R., & Fink, G. R. (2013). Transcranial Direct Current Stimulation (tDCS) of Left Parietal Cortex Facilitates Gesture Processing in Healthy Subjects. *Journal of Neuroscience*, *33*(49), 19205–19211. https://doi.org/10.1523/JNEUROSCI.4714-12.2013

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., … Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *127*(2), 1031–1048. https://doi.org/10.1016/j.clinph.2015.11.012

Wozny, D. R., Beierholm, U. R., & Shams, L. (2008). Human trimodal perception follows optimal statistical inference. *Journal of Vision*, *8*(3), 24. https://doi.org/10.1167/8.3.24

Wright, J. M., & Krekelberg, B. (2014). Transcranial direct current stimulation over posterior parietal cortex modulates visuospatial localization. *Journal of Vision*, *14*(2014), 1–15. https://doi.org/10.1167/14.9.5.doi

Zaghi, S., Thiele, B., Pimentel, D., Pimentel, T., & Fregni, F. (2011). Assessment and treatment of pain with non-invasive cortical stimulation. *Restorative Neurology and Neuroscience*. https://doi.org/10.3233/RNN-2011-0615

Zhao, H., Qiao, L., Fan, D., Zhang, S., Turel, O., Li, Y., … He, Q. (2017). Modulation of

Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS): Clinical Applications and Safety Concerns. *Frontiers in Psychology*, *8*, 685. https://doi.org/10.3389/fpsyg.2017.00685