Effect of tACS on Motor Performance and Adaptation during a Bimanual Task

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Date:__________________________________

Signature (HOD):________________________

Date:__________________________________

Signature (Principal):_____________________

Date:_________________________________

Dedicated to, My mother Nasreen Fatima and my siblings specially Mariam shah

Copyright Statement

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Abstract

Transcranial Alternating Current Stimulation is a non-invasive modality to alter neural activity in a frequency specific manner. The present study aims at investigating the effects of cerebellar tACS in inducing plasticity and motor adaptation Purkinje fibers are present in cerebellum and project into deep cerebellar nuclei that are the only output of cerebellar cortex that oscillate at natural frequency of 50 Hz. Cerebellum was stimulated at 50 Hz frequency targeting purkinje fibers at an intensity of 2mA for 18 minutes.it was applied long enough to induce neuroplastic effects. In our study Motor adaptation and performance was evaluated using two different tasks. Task A was tapping task that had the in-phase and antiphase tapping of index fingers on low and high frequency audio cues. Whereas task B was button press task with single audio cue and pressing twice the push button and a pulse transducer. Results were visually analyzed and group comparison was made using ANOVA.33 people took part in the study 11 were given active stimulation, 11 were sham and 11 were control group It was double blind sham controlled study and the data suggest that tACS group performed better than the control group or the sham group in early session whereas it performed better than the sham group in late sessions.

Keywords

Cerebellar tACS, motor adaptation, neuroplastic effects, double blind, sham-controlled, Purkinje fibers,ANOVA.

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1 Introduction

tES is a non-invasive way to alter cortical excitability by means of electrodes attached to the scalp. tDCS uses direct current in which the direction of the current over the time remains constant. tACS uses alternating current which can be a sinusoidal wave or any of the other shapes that exclude DC offset. Alternating current is provided via electrodes using one electrode is active and other as reference electrode. Different electrode montages are possible and are being actively researched for different therapeutic, rehabilitative and research purposes.

1.1 Motor learning paradigms

Different motor learning paradigms include serial reaction time task SRTT, visuomotor task and finger tapping task etc motor learning paradigms are used to assess motor learning, adaptation and reaction times for different purposes here we choose finger tapping task to evaluate effect of tACS on motor performance and adaptation in a bimanual task.

1.2 tACS

Transcranial alternating current stimulation entrains ongoing neural oscillations in the brain in a frequency specific manner. Alternating current is used as the name indicates as the modality in the procedure. Very scarce literature is present on tACS rather tDCS is more reported than the tACS which has only now begun to be researched. tACS is used for a definite period of time with a definite amplitude and frequency.

1.3 Cerebellar tACS

Cerebellum is the most important part of the brain when it comes to coordination and control. Cerebellar tACS induces plasticity and effect the motor learning in remote network manner. Plasticity is induced in the networks which results in downscaling of inhibitory effects of purkijie fibers on the motor cortex and increase in motor evoked potential is recorded.

1.4 TMS

Transcranial magnetic stimulation is used in most study with tACS to evaluate different parameters such as Motor evoked potential MEPS, Cortical Silent Period CSP, Cerebellum brain inhibition CBI.

1.5 Neuroplasticity

Neuroplastic means that neurons that fire together wire together it is the Hebbian rule. And property of the brain that it is dynamic in nature new connection are formed and old are lost, as the two neurons that are connected to each other fire together the cohesiveness between them is increased and two neurons that seldom fire together they are less keen to make new connections.

2 Literature Review

Non-Invasive brain stimulation techniques (NIBS) is a novel way to trans-cranially deliver electric charge or electric field through the scalp via electrodes or coils kept at a certain angle to deliver supra-threshold or sub threshold extracranial oscillations and have provided modalities to explore brain-behavior relationship by modulation of different cerebral areas and develop remedies for psychiatric disorders. Brain-behavior relationship is loosely defined via TMS studies over past 25 years of research and EEG studies. NIBS provide not only online effect one that is measured during electrical stimulation but also substantial offline effects, one that are measured after the stimulation, for long durations. Electromagnetic modalities can affect neural population activity either electrically or magnetically and is known as Transcranial electric stimulation and transcranial magnetic stimulation .(Yavari, Jamil, Samani, Vidor, & Nitsche, 2018) TES is an umbrella term that covers tDCS, tACS, and TMS based on the non-invasive modality of applied electric current.(Yavari et al., 2018) TES tools are generally more

- affordable,
- easier to work with,
- non-invasive,
- Compliance to different testing paradigms is easier.

Transcranial direct current stimulation is the most widely reported form of tES that delivers weak direct current over scalp by means of two or more electrodes.

2.1 Transcranial alternating current stimulation

tACS delivers alternating current usually without aDC offset whereas tRNS is a specific type of tACS that involves delivery of current that fluctuates between 0.1-640 HZ and has a white noise characteristic. If oscillations are introduced to direct current it is known as oscillatory tDCS. The shape of alternating current can be variable it can be as complex as rectangular wave it is not necessary that it should be sinusoidal wave.(Herrmann, Rach, Neuling, & Strüber, 2013) The major functions that can affect the duration and direction of tACS effects are intensity of the stimulation, frequency and phase of stimulation and electrode montage(Antal & Paulus, 2013),(Mehta, Pogosyan, Brown, & Brittain, 2015) The active electrode is placed on a single foci on the cortical region whereas the second electrode required to complete the circuit is known as reference electrode and it's larger in size as compared to the active electrode in order to dissipate current. Keeping the active electrode at the same position and changing position of reference or return electrode effects the physiological entrainments.(Mehta et al., 2015)

2.2 Frequency of stimulation

TACS can be applied in a wide frequency range between DC to 5 kHz using a single frequency however combination of different frequencies is possible. A suitable target in the cerebellum is represented by Purkinje cells which exhibit the intrinsic neuronal frequency of 50 Hz that is our targeted frequency.(Naro et al., 2018)Purkinje cells are Golgi Type 1 neurons that are arranged in a single row and are flask shaped with dendrites passing into molecular layer of the cerebellar grey matter and axon projecting onto the dentate nuclei that is an intracerebellar nuclei embedded in the white matter of cerebellar hemisphere and the axons of dentate nuclei form the superior cerebellar peduncle that connect the cerebellum to midbrain from where the axons of purkinje pass and terminate into thalamic nuclei which are directly connected to primary motor cortex M1(Richard S. Snell, 2010)and influence their excitability by reducing the facilitatory tone of the dentate-thalamocortical pathway(Naro, Bramanti, et al., 2017). Retinal phosphenes are induced in the lower frequency range of 10-40 Hz and intensity of 250µA(Paulus, Peterchev, & Ridding, 2013).

2.3 Intensity of stimulation:

The effect of tACS seems intensity dependent. Different studies show that A.C. with low intensity but different frequencies allow inhibition of M1.Inhibitory circuits can be excited with lower intensities up to 1mA.(Antal & Paulus, 2013)Stimulation devices deliver a predefined amount of electric current (I), measured in (mA). According to Ohm's law (V=IR) voltage required to produce a specific intensity current depends upon the resistance between the two connectors on the device. Since the R of wires and electrodes is very low the main resistance in the system comes from the interface between the electrodes and the biological tissue.(Noah S. Philip et al., 2017) Maximum Voltage for cerebellar stimulation is 10-20 V and intensity selected is 2mA.(Naro et al., 2018)A large intensity of current is shunted away by the skin that is a good conductor so it doesn't influence the intracranial current density. Nonetheless significant electric field density can be modelled intracranially that result from transcranial stimulation.

2.4 Phase of stimulation

The extra cranially applied alternating current has a phase that entrains the intrinsic neuronal activity in a phase specific manner. This modification in phase of intrinsic neuronal spike can be avoided by phase locking but this modality is not being practiced yet in our lab(Nakazono, Ogata, Kuroda, & Tobimatsu, 2016).The soma of neuron is less susceptible to electric field than theAxon-Hillock and it has been demonstrated that electric fields that are in parallel to axonare much more effective than those at 90 degrees to the them.

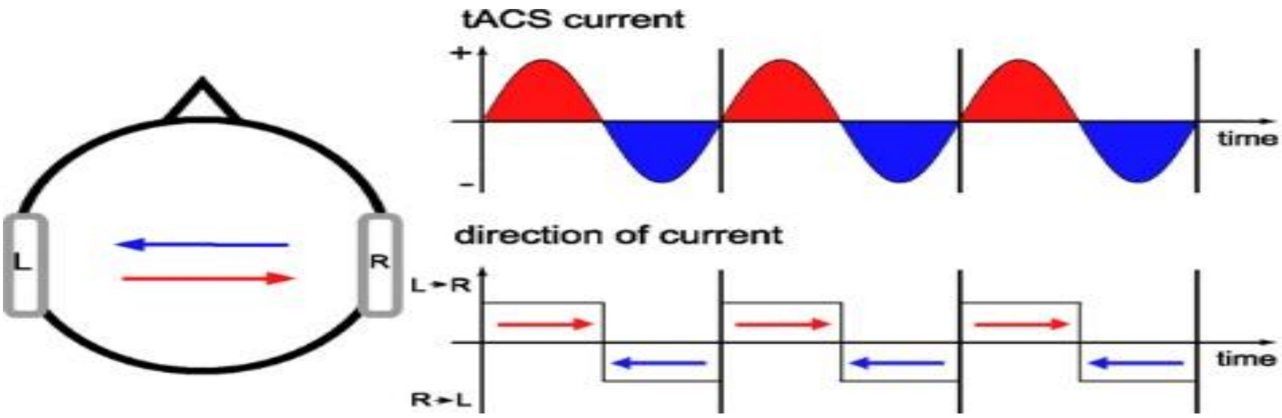

Figure 2.1tACS current where phase or direction of the current changes by 180 degree and the current is also not constant in that duration whereas blue and red show the direction of current gray coulour shows the electrodes.

2.5 Electrode montage

The active electrode is of course positioned over the area of interest whereas the reference electrode or return electrode is oversimplified and taken as granted but its position may well over influence the experimental paradigm. While working with physiological tremors Mehta et al, showed that only the right shoulder position was significant because of the entrainment it produced. (Mehta et al., 2015)Since head exhibits heterogeneous electrical properties and when the current is delivered large part of the current does not penetrate the skull and is shunted away. By keeping the active electrode at right cerebellum and reference electrode at the ipsilateral buccinator muscle or the ipsilateral shoulder since it has been shown that active electrode over the primary motor cortex generated significant entrainment.

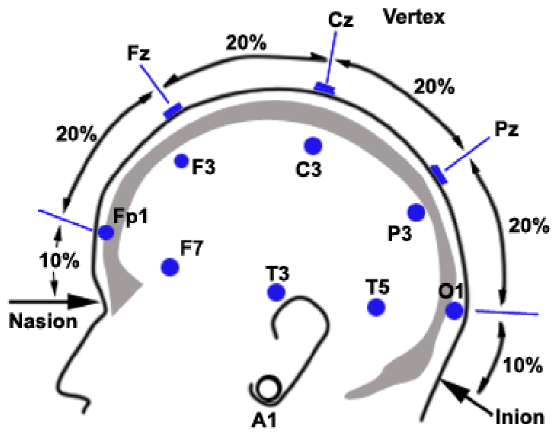

Figure - Electrode placement according to 10-20 System

2.6 Duration

The effect of tacs duration on MEPs have not been systematically investigated yet and is usually taken as it is from previous research. tACS is able to modulate electroencephalography oscillations during time duration of stimulation. Mechanism of tACS has been discovered in ferrets and rats and none of the literature reports the lasting effects of the stimulation as soon as the stimulation was removed observed effects were lost (Strüber, Rach, Neuling, & Herrmann, 2015).

2.7 Mechanism of tACS

The physiological mechanism underlying tACS is not well understood yet however one hypothesis that have been suggested is the entrainment of brain oscillations by tACS and another hypothesis is that tACS leads to synaptic changes via spike timing dependent plasticity mechanism. There are online effects of stimulation i.e those that are present during the stimulation and offline effects i.e those present after the stimulation and both of them have been studied by various animal models. Recently the mechanism underlying tACS have been revealed via intra cranial recordings in ferrets in which MUAs and LFPs were recorded. Cortical slices were stimulated in vitro and multi-unit activity was recorded that showed that entrainment depend upon the maximum voltage of applied field and also on the temporal sequence. It was revealed that weak sinusoidal voltage were able to elicit spiking activity and the spiking activity can be synchronized to frequency of electric field thus controlling the spiking activity.(Paulus et al., 2013),(Fröhlich & McCormick, 2010)And it showed its dependency on temporal sequence as the steep transient voltage changes lead to stronger neural firing than slow transient changes that reach the same maximum voltage .(Fröhlich &

McCormick, 2010)To achieve 1V/m intracranial field,the extracranial current that has to applied is affected by various factors such as scalp thickness(Paulus et al., 2013). AC stimulation up and down regulate the firing rate in an oscillatory manner without changing the average firing rate over a long period of time interval.AC stimulation at the frequency of endogenous oscillations mainly affects spike timing dependent plasticity after stimulation.

2.8 Entrainment

Temporal alignment of the intrinsic brain activity to exogenous electric stimulation is known as entrainment. TACS-induced entrainment has been demonstrated during tACS both behaviorally and electrophysiologically in humans as well as in animal studies both in vitro and in vivo. The latter work was done in humans in which photic stimuli were given and EEG was obtained where the frequency of activity recorded was time locked to flash frequency during photic stimulation and it indicated that entrainment is strongest when stimulation frequency is at or close to the natural resonant frequency of the network that is its Eigen frequency. Specifically the stimulated system is then expected to respond at the driving frequency rather than its Eigen frequency (Vossen, Gross, & Thut, 2015).

2.9 Spike-timing-dependent-plasticity (STPD)

Another mechanism is spike-timing dependent plasticity (STPD) that adjust the strength of the connection of the neurons. In STPD, long term potentiation or long term depression occur depending upon the time and magnitude of firing of neuron. If presynaptic neurons fire few milliseconds before the postsynaptic neuron then long-term potentiation (LTP) will occur and it will lead to the strengthening of neuronal connection. When presynaptic neurons fire, glutamate is released in the synaptic cleft that binds to AMPA receptors and open them and when they open depolarization occur in the postsynaptic neuron that displace magnesium away from NMDA receptor thus activating it that lead to large calcium influx and this large calcium influx will activate kinases leading to increase recycling, exocytosis and phosphorylation of AMPA receptor. Zahele et al (Zaehle, Rach, & Herrmann, 2010) used a neural network model where a single externally driven neuron was connected to various other neurons having varying delay times that lead to formation of different resonant circuits and in this model when a continuous 10 Hz frequency was given, it only modulated those resonance loops having frequency close to resonance frequency (Vossen et al., 2015). However, long term depression (LTD) occurs if the presynaptic neurons fire few milliseconds after the post synaptic neuron because in this case the postsynaptic neurons will be in repolarization phase so magnesium will not be displaced from NMDA receptors so a small amount of calcium will enter that activate phosphatase leading to increased endocytosis of the AMPA receptors.

There are different speculation about both the mechanisms and some indicate that entrainment occurs as an online effect whereas spike-timing dependent plasticity occur as offline effects

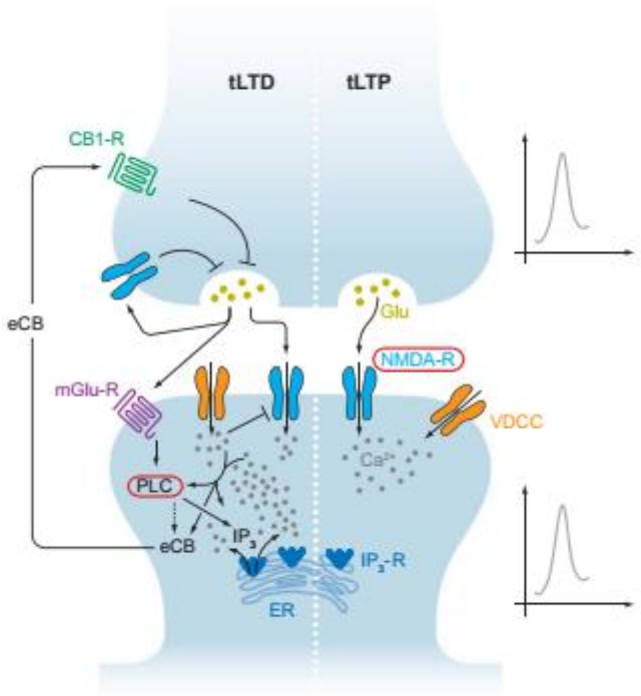

Figure 2.2- Receptors that take part in LTP or ltd right and left respectively

2.10 Motor System

Motor execution is a complex process and to execute motor activities in a precise and coordinated way the motor system has to do varying function such as sensory perception, decision making and other associated functions and for organization of these function cortex, cerebellum, striatum, spinal cord and thalamus are involved (Reis, Prichard, & Fritsch, 2014).

Hence the motor system comprises many subsystems that are often co-activated to bring about a particular task because the functions of this subsystem are interrelated. The components of motor system are primary, pre and supplementary motor cortices, cerebellum, striatum and thalamus. (Reis et al., 2014) Alpha and Beta Oscillations in the motor cortex have been assessed by applying 10 or 20 Hz tACS at 1mA for 10 min through 35cm electrodes movement speed and accuracy of the right hand during a finger tapping task were assessed at different time t0, t30, t60 minutes, In addition CSP and TMS elicited MEPs were evaluated. 10 Hz increased movement variability and 20 Hz tACS resulted in movement slowing. These effects were present at different time-points: immediately after stimulation for 20 Hz and 30 min after tACS for the 10 Hz stimulation.(Wach et al., 2013)Cerebellum-brain interactions can be assessed using TMS by CBI paradigm can assess the inhibitory effect of the cerebellum on the contralateral M1 excitability. At rest, dentate nuclei are being both excited and inhibited but this is balance is in favors of excitation so even at rest the dentate nuclei continuously stimulate the motor cortex M1.for the motor execution when the input is sent from cerebrum to the respective joint ,collateral also passes to cerebellum that increases the firing rate of deep cerebellar nuclei by way of mossy and climbing fibers that enhances the motor activity by turning on the agonist and turning off the antagonist however after a fraction of second an inhibitory impulse arises that decrease the firing level of dentate nuclei that help to stop the movement from overshooting its mark and this inhibitory impulse arises by the way of inhibitory interneuron (purkinje cell).Tms decreases the M1 excitability by decreasing the firing level of dentate nuclei and this is done by stimulating the purkinje that act as inhibitory interneuron .(Naro, Milardi, et al., 2017)For the motor sequence learning and adaptation initially a dynamic interaction between areas such as Striatum, cerebellum, motor cortex, prefrontal, parietal, and limbic is required. however lately two different pathways operate .For the motor sequence learning the striatum is involved and information is transmitted from associative areas to the striatum and after consolidation the striatum has the representation of the task however for motor adaptation the other pathway operate and striatum is not involved instead of that information passes from associative area to cerebellar nuclei and after consolidation the representation of the neural pathway for motor adaptation is on cortical network that involve cortico-cerebellar circuit.(Doyon & Benali, 2005)

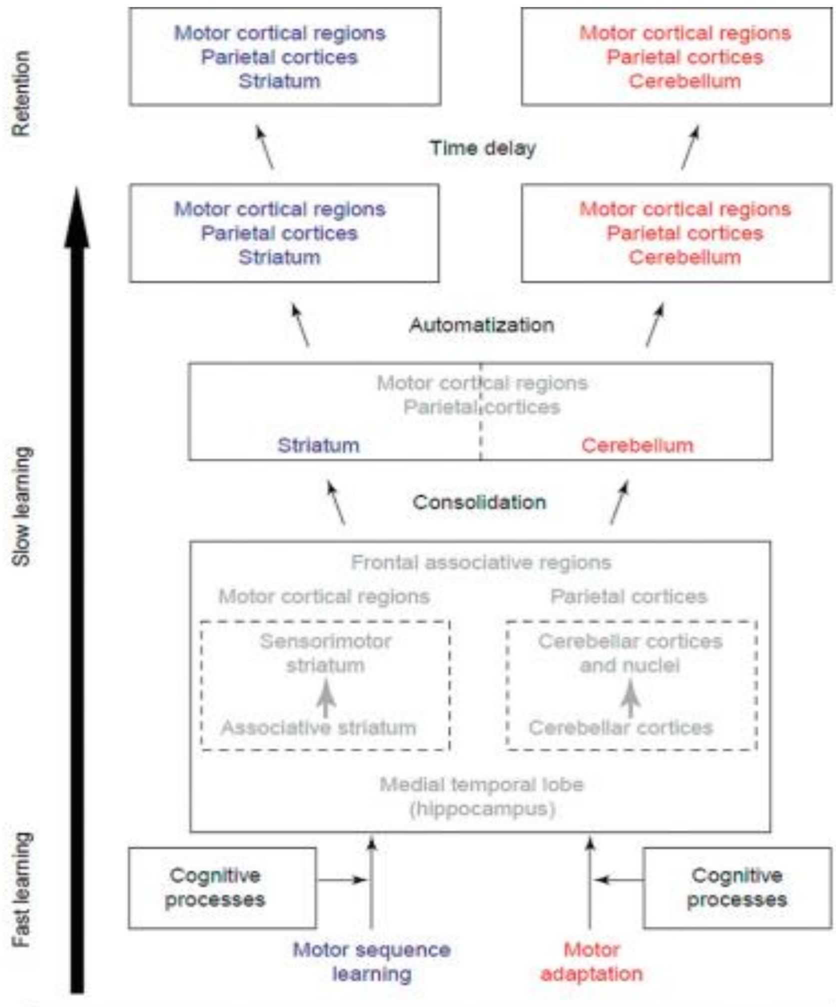

Figure 2.3- Motor adaptation and the areas required

The effect of TES can be measured either behaviorally by reaction times and performances etc. or it can be measured EEG, MEG, or EMG. A standard to measure the effect of TES is to recorded. Motor evoked potential over the M1 by single pulse TMS.(Antal & Herrmann, 2016)

2.11 Sensorimotor Synchronization

It is a referential behavior in which action is temporally coordinated with predictable external event known as referent. Usually, the action synchronizes with the referent in such a manner that it becomes predictable with each recurring referent and thus it can be defined as coordination of motor rhythm with external rhythm(Repp, 2005). Understanding the neurobiological role of cerebellum in SMS is of prime importance. Although lesions studies focus on cerebellum, basal ganglia, and frontal parietal structures as key structure in time keeping function. Cerebellar cortex is considered as important in timing the interval between the stimulus and learned response.(Molinari et al., 2005)

2.12 Tapping task

Fast finger tapping task has been performed by (Wach et al., 2013) and their result showed behavioral variability with 10 Hz and movement slowing with 20 Hz . Another study performed by (Naro et al., 2018) using finger opposition and stimulating cerebellum at 3 different frequencies showed that increase motor performance at 50 Hz. While there has been no significant literature about bimanual finger tapping task and tACS, thus bimanual finger tapping task has been selected for the present study. Tapping task are of two types on the basis of internal or external stimuli that are given so that all the subjects perform the learning paradigms at a predetermined rate. Pacing stimuli is used in conjunction with complex tasks such as bimanual tasks. According to the fMRI studies the main effect of such tapping tasks is over primary sensorimotor cortex (SM1), Supplementary Motor area (SMA), basal Ganglia and cerebellum. Regions in cerebellum have been shown to be active during the preparation, execution and timing of both simple and complex movements. It has been observed in motor tasks driven by both internally and externally paced stimuli.(Witt, Laird, & Meyerand, 2008)

2.13 Button press Task

Tapping task induces plasticity whereas stimulation helps attain this plastic state button press was thoroughly evaluated for error reduction by visually analyzing the peaks and the button press made in time duration of response time and stringent criteria was used to include correct number of tap. Button press task included pressing of a push button twice and a pulse transducer once.

2.14 Objectives

- Evaluation of offline effect of tACS on a subsequent motor task.
- Evaluation of online tACS effects during the tapping task
- Induction of practice driven plasticity for performing subsequent motor task.

2.15 Hypothesis statement

50 HZ tACS effect motor performance and adaptation during bimanual tapping task.

3 Materials and Methods

3.1 tACS

Transcranial alternating current stimulation of about 2mA for a duration of about 18 mins was provided to the subjects. Frequency of the current was 50 Hz and the device foc.us was used in bipolar mode. The active electrode was placed on the cerebellum 2-3 cm down from the inion and 3-4 cm laterally from the inion according to the 10-20 system. Whereas reference electrode was placed on ipsilateral buccinator muscle. The device was operated in 10 V. Hydrogel based electrode were used with the surface area of 5*5 cm

Figure 3.1- tACS foc.us V2

3.2 Subjects

Subjects were seated in a comfortable chair and were provided with resistive touch pads, pulse transducer and button press. The study was double blinded and sham controlled. Subjects were provided with consent forms and screening forms. About 20 subjects were selected on the basis of criteria defined by screening forms and were duly reported about the experiment protocol both, verbally and in written form. The protocol was accepted by the local ethical committee. Skin was prepared using alcohol swabs and was inspected for any cut or lesion before the electrodes were attached

3.3 Experimental Overview

Subjects were seated comfortably in a chair at some length from the screen. Subjects were asked to tap on a resistive touch pad sitting in a comfortable chair. Electrodes were attached to the cerebellum and ipsilateral buccinator muscle using plastic bands.

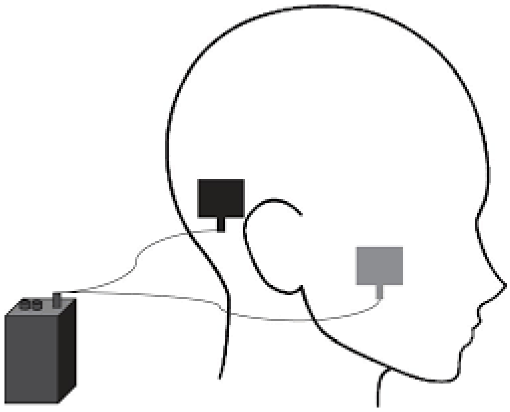

Figure 3.2- Active and reference electrode

The protocol had two bimanual tasks, finger tapping task and a button press task. Former was used to induce plasticity and later was used to probe the effects of practice driven plasticity and learning of a new motor task. Whereas tACS also modulated neural oscillation in a frequency specific manner and both the task were also being used to evaluate motor learning and motor adaptation during both the tasks.

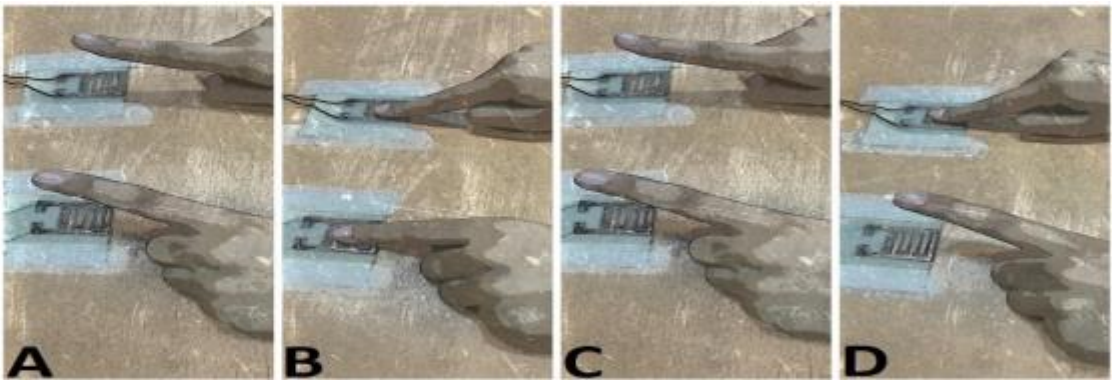

Figure 3.3- A: Initial Position , B in-phase tapping C: initial position D: anti-phase tapping

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3.4 Signal Acquisition

The hardware used to convert analogue system to digital signal was power lab® by AD instruments. Power lab is a simple, user friendly tool which is used to record and analyze data acquired from physiological signals. It allows recording from 4 channels at a time. Power lab has a system time lag of 50-60msec mentioned in the user manual of the hardware. After acquisition analogue data is sampled, amplified filtered and displayed as a digital signal by a software known as Lab Chart. Macro was used to provide beeps and no external trigger was used for that purpose. ‘

3.5 Tapping task

Analogue signals from two resistor touch sensors are fed into channel 1 and 2 of the power lab through BNC connectors.

3.6 Button press task

For button press task signals were acquired through pulse transducer (AD Instruments) and push button (AD Instruments). Channel 1 and 2 are used for both the instruments.

3.7 Experimental Setup

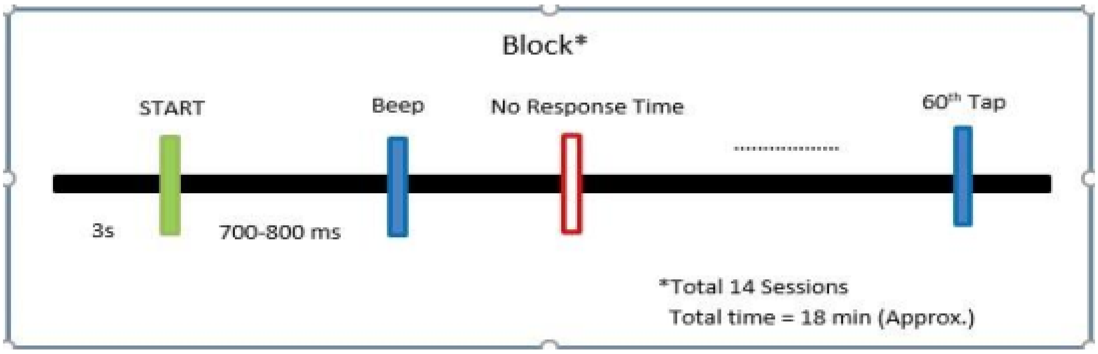

Figure 3.4- Block Diagram Tapping task

3.8 Tapping task

Subjects were seated in a comfortable chair and were instructed to carry out bimanual finger tapping adopted from (Serrien, 2009) and tACS was used for the duration of tapping task which is 18 minutes. Tapping was done with index fingers on locally made resistor touch sensors. Subjects were asked to use the index finger for tapping that was done on a locally made resistor pad and they were instructed to tap both index fingers followed by tap of non-dominant index finger while keeping the dominant index finger at peak position which is actually 2:1 mode. Timing was internally paced and auditory stimulus (beep)was generated in between 700-800ms using macro present in Lab Chart software. An auditory cue (beep) at the start of the task after 3s represented the beginning of the task. The task itself had 14 sessions with 60 taps per session. Simultaneous tapping should be done in response to low frequency beep followed by tapping of non-dominant index finger at high frequency beep. Subjects were instructed to tap immediately after hearing the beep within the response time of 400ms.

3.9 Button Task

Task B had 7 sessions of 30 trials each with no break in between the session. In each trial subjects were asked to perform tapping on a transducer (ADInstruments, Australia) with the index finger along with twice pressing the push button (ADInstruments, Australia) with thumb of non-dominant hand. Instantly after hearing a beep, timing was internally paced and auditory stimulus with inter trial interval of 550-650 ms was generated using the macro in Lab Chart software

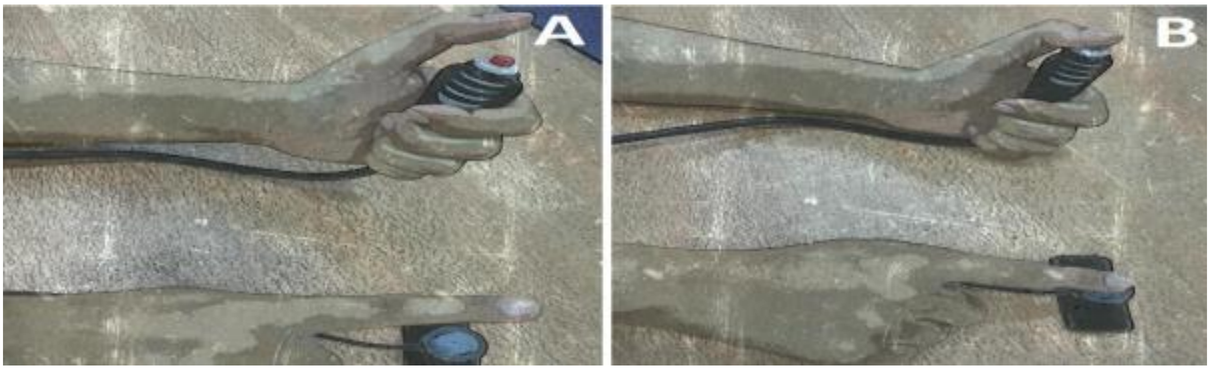

Figure 3.5- Button press Task

Subjects were instructed to perform the task immediately after hearing beep and synchronize their tap with the second button press. Lab Chart software (ADInstruments, Australia) was used to record data in all tasks. The data was stored for further analysis.

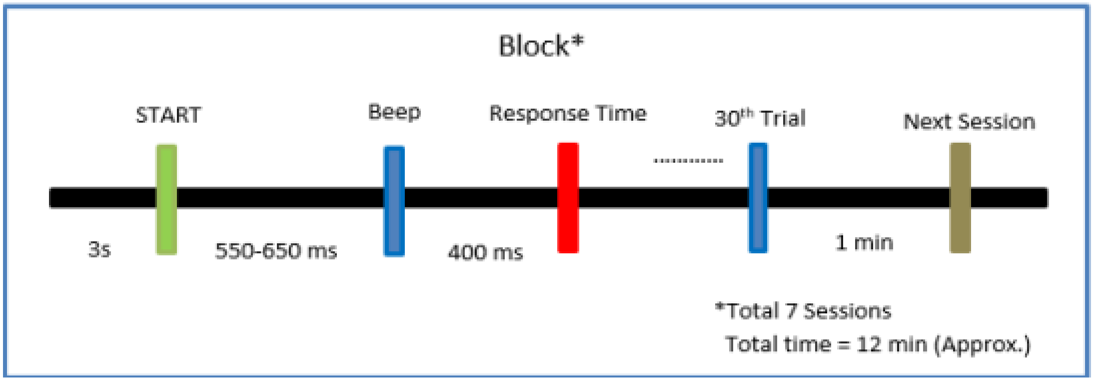

Figure 3.6- Block Diagram Button Press task

4 Results

Data was divided into early and late session and scores were averaged to calculate correct number of trials. 33 individuals were analyzed with 11 active group, 11 sham and 11 control group. The study was purposely a sham-controlled study and was double blinded. One way ANOVA was applied to the early sessions learning period of the study and results are as followed

4.1 Early Session- Button Task

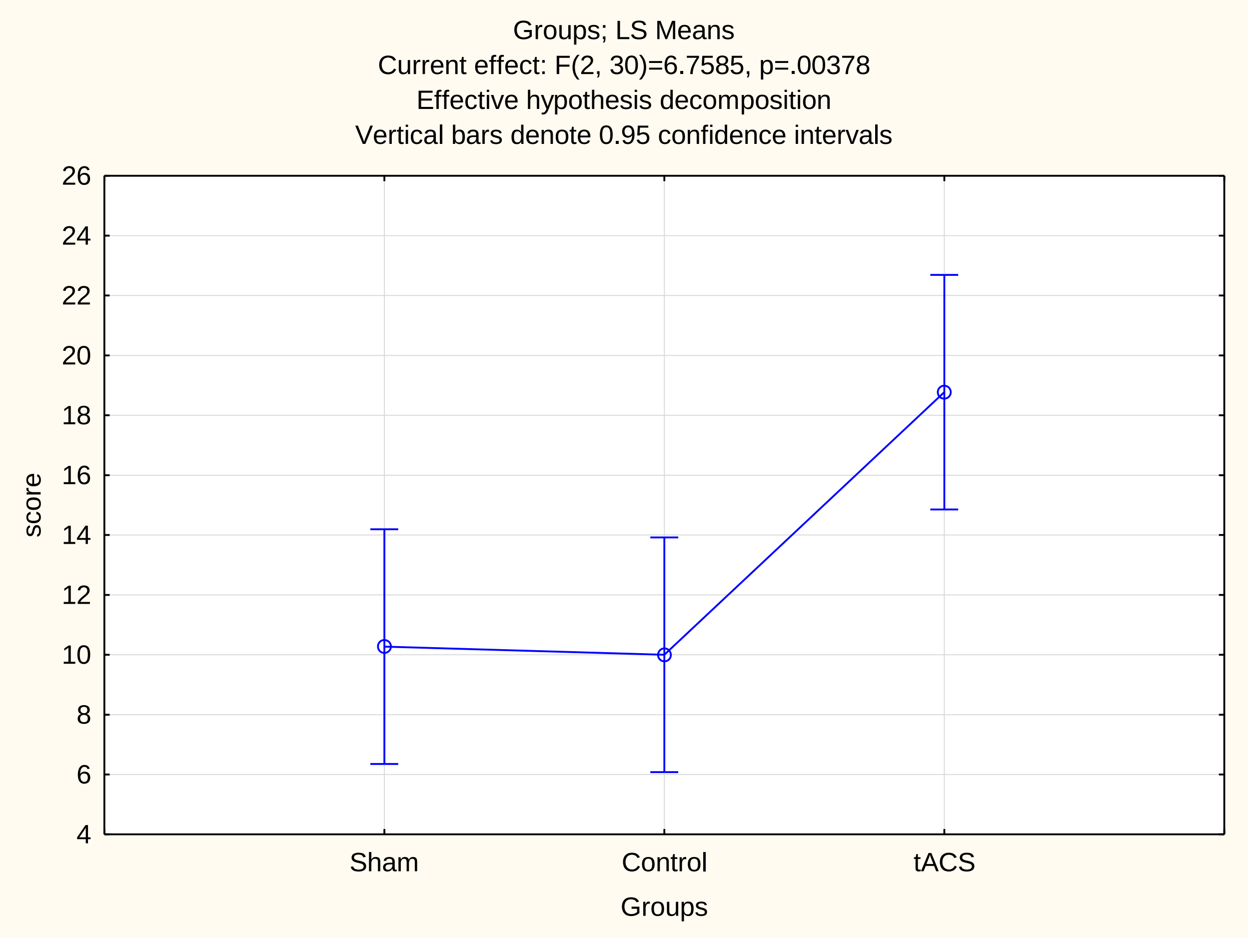

Figure 4.1-P value = 0.0378 that is a significant value

P Value is 0.0378 which is significant which show that there is significant difference among the groups and tACS group performed much better than the control or the sham group. Following are the mean scores of early stage of groups.

Cell No.	Groups; LS Means (Early session.sta) Current effect: F(2, 30)=6.7585, p=.00378 Effective hypothesis decomposition Groups	score Mean	score Std.Err.	score -95.00%	score +95.00%	N
1	Sham	10.27273	1.918699	6.35422	14.19123	11
2	Control	10.00000	1.918699	6.08149	13.91851	11
3	tACS	18.77273	1.918699	14.85422	22.69123	11

Figure 4.2-Mean scores of the analysis

4.2 Post-hoc test

Post-hoc test signifies that there is a significant difference between the sham-control and the tACS group. Whereas tACS group performed better than the sham or the control group.

	Tukey HSD test; variable score (Early session.sta) Approximate Probabilities for Post Hoc Tests Error: Between MS = 40.495, df = 30.000			
Cell No.	Groups	{1} 10.273	{2} 10.000	{3} 18.773
1	Sham		0.994525	0.010546
2	Control	0.994525		0.008228
3	tACS	0.010546	0.008228	

Figure 4.3-Post-hoc analysis of early sessions groups

4.3 Late Sessions:

In the late sessions, again one–way Anova was applied.

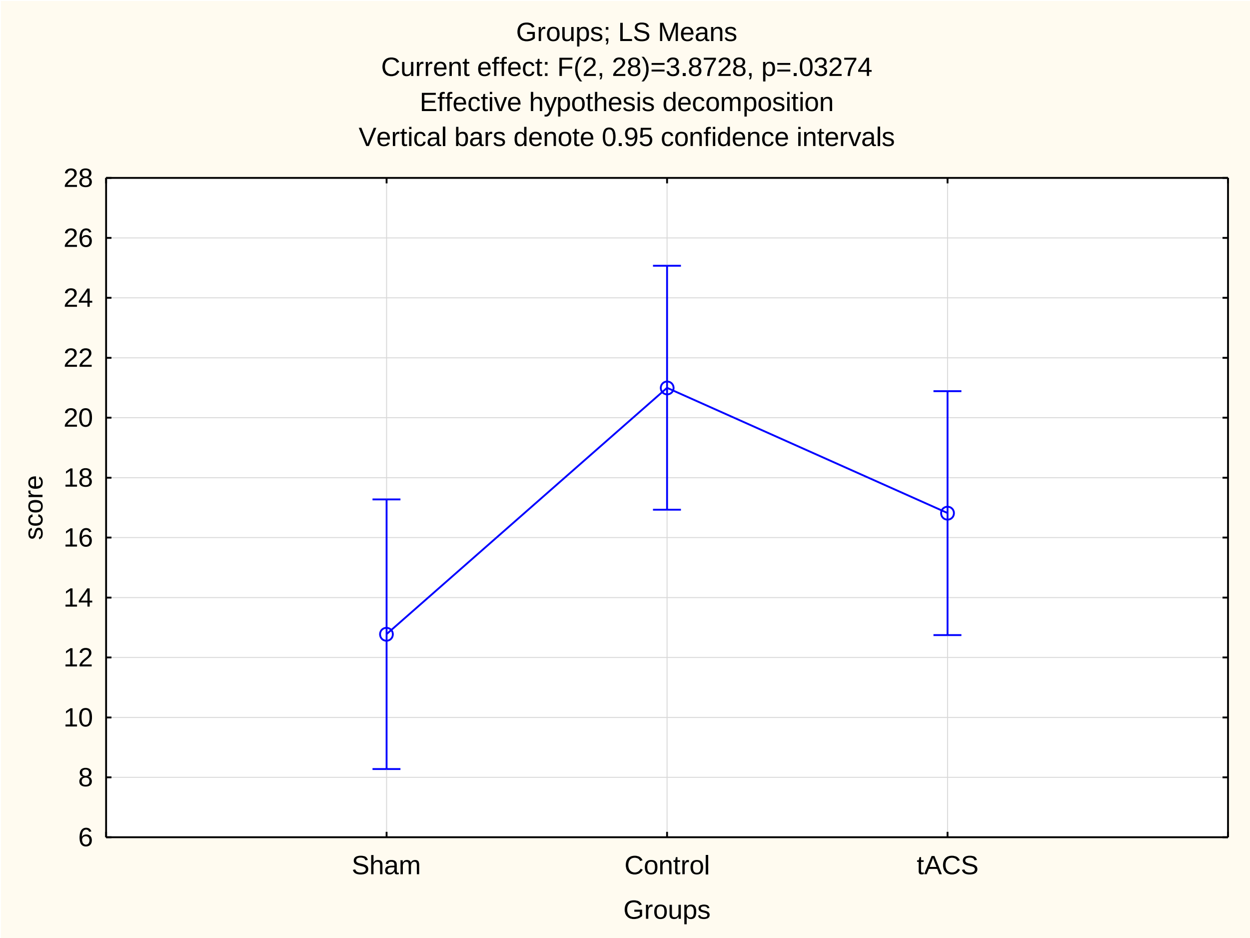

Figure 4.4-Late Session ANOVA

Cell No.	Groups; LS Means (Late session.sta) Current effect: F(2, 28)=3.8728, p=.03274 Effective hypothesis decomposition					
	Groups	score Mean	score Std.Err.	score -95.00%	score +95.00%	N
1	Sham	12.77778	2.196400	8.27866	17.27690	9
2	Control	21.00000	1.986719	16.93039	25.06961	11
3	tACS	16.81818	1.986719	12.74857	20.88779	11

Figure 4.5-Mean scores of late sessions

Cell No.	Tukey HSD test; variable score (Late s Approximate Probabilities for Post Hoc Error: Between MS = 43.418, df = 28.0 Groups	{1} 12.778	{2} 21.000	{3} 16.818
1	Sham		0.025569	0.37294
2	Contro	0.025569		0.31171

Figure 4.6-Post hoc analysis

4.4 Tapping results

Early session tapping task

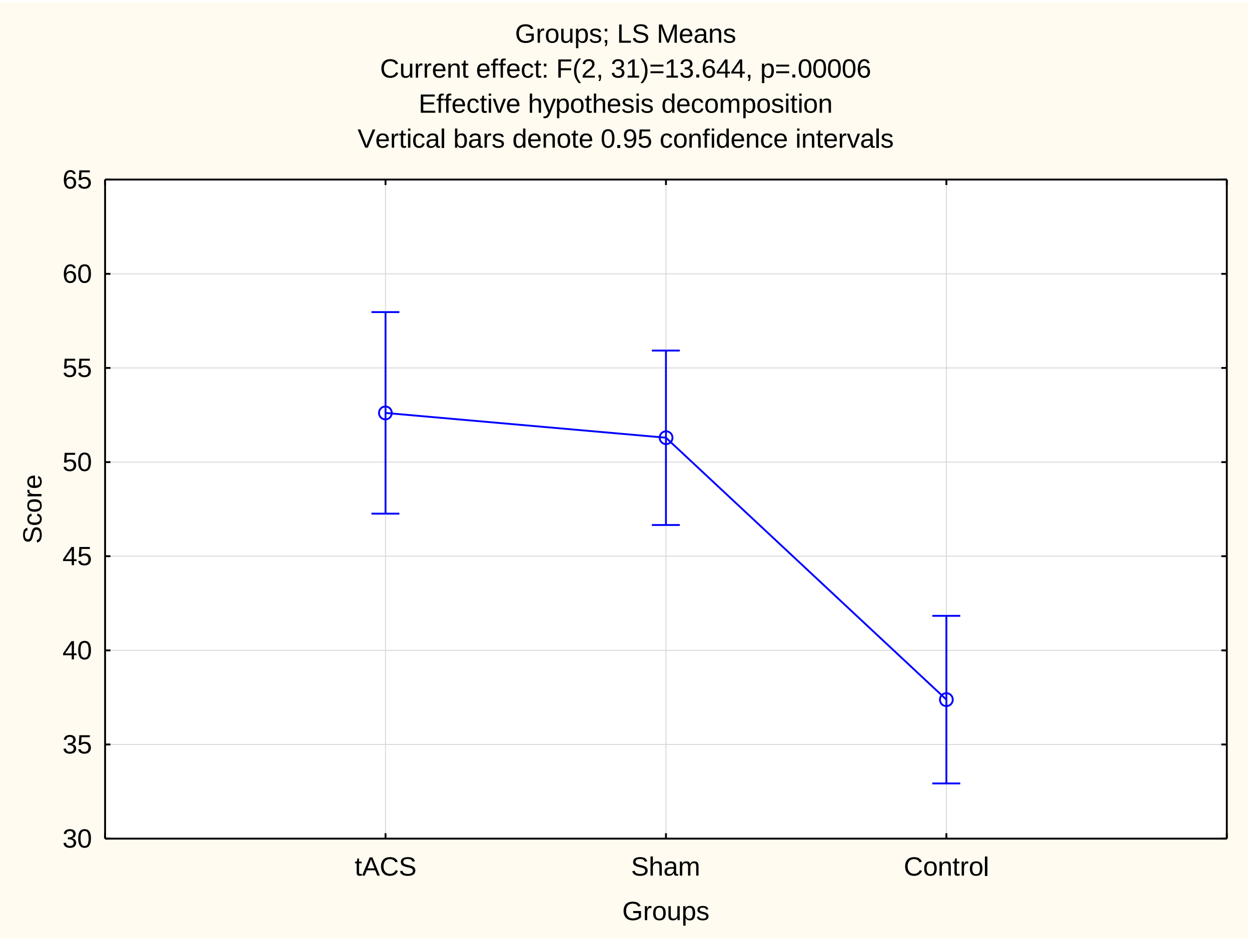

Figure 4.7-Early Session Tapping Result

Cell No.	Tukey HSD test; variable Score (early.sta) Approximate Probabilities for Post Hoc Tests Error: Between MS = 61.958, df = 31.000 Groups	{1} 52.611	{2} 51.292	{3} 37.385
1	tACS		0.923706	0.000392
2	Sham	0.923706		0.000432
3	Control	0.000392	0.000432	

Figure 4.8-Tukeys's Test

Cell No.	Groups; LS Means (early.sta) Current effect: F(2, 31)=13.644, p=.00006 Effective hypothesis decomposition Groups	Score Mean	Score Std.Err.	Score -95.00%	Score +95.00%	N
1	tACS	52.61111	2.623778	47.25988	57.96234	9
2	Sham	51.29167	2.272258	46.65736	55.92597	12
3	Control	37.38462	2.183115	32.93212	41.83711	13

Figure 4.9-Means of al results

4.5 Late Session tapping task:

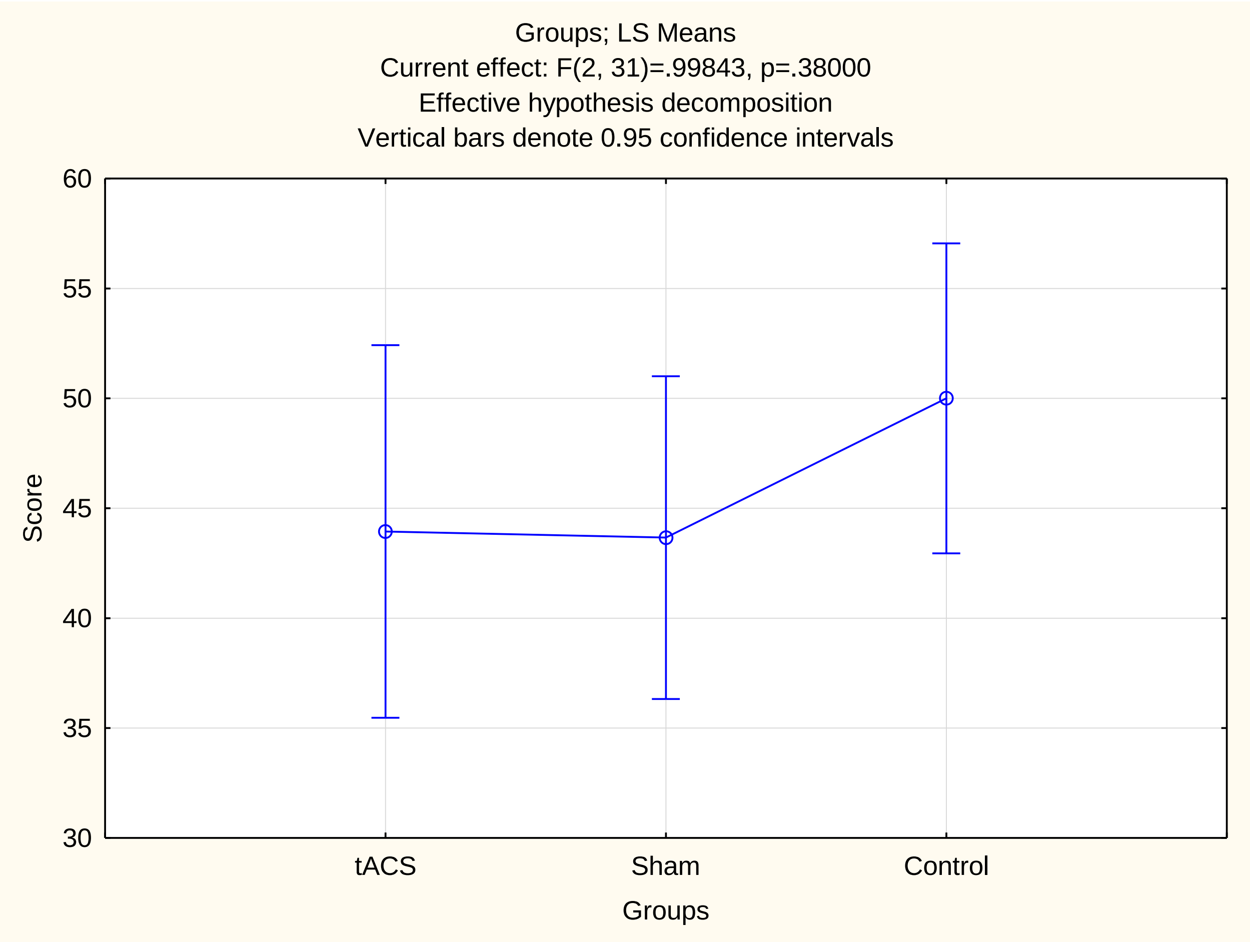

Figure 4.10-Anova Results for all conditions

5 Discussion

Cerebellar tACS at 50 Hz, 2mA and for 18 minutes induces plasticity that can be analyzed using finger tapping task. The main idea behind all of the study was to check whether or not tACS induces plasticity and can increase motor performance and adaptation in an otherwise lengthy bimanual task. Whereas (Wach et al., 2013) performed fast finger tapping 10 HZ and 20 HZ showed movement variability and slowing with tACS respectively. whereas (Naro et al., 2018) showed 50 Hz frequency better the motor performance in a finger opposition task. No study so far has reported effect of tACS on bimanual skill acquisition or motor plasticity in that regard. Ipsilateral buccinator muscle was used as a reference as did by (Mehta et al., 2015). Cerebellar tACS at 50 Hz stimulates the purkinje fibers in the cerebellum which has effect on cerebellum brain inhibition. The study includes bimanual finger tapping from healthy individuals from whom consent was taken and they were screened for any anomaly. Results showed that indeed the Individuals with tACS stimulation performed better than the sham or the control individuals. In the late session score were not significant for tACS group, althoughit performed better than the sham group but not from the control group because of inter personal variability of tapping although tACS group still performed better than sham group. It didn’t perform significantly better than the control group.

5.1 Motor learning

It has been shown prior that tapping task implies plasticity in brain which can be carried to the subsequent motor task. in our study motor learning was shown in the individuals with active tACS and the spike timing dependent plasticity mechanism was proposed for the learning of novel skill that is in-phase and antiphase tapping

5.2 Demerits of the study

- Learning in the tapping task couldn’t be studied because of the nature of the resistive touch pads and associated noise.
- The tACS signal couldn’t be phase locked to the brain oscillations
- Concurrent EEG couldn’t be performed
- Data was analyzed visually
- Tapping Task was lengthy and exhaustive
- Audio cues were seldom discernable

- TMS was not available

5.3 Merits of the study

- Bimanual finger tapping , no other study has yet explored the area of bimanual finger tapping.
- 50 HZ tACS stimuli because it matches natural oscillation of purkinje fibers.
- Every sensor for example resistive touch pads were made indigenously or by the AD Instruments Australia which were readily available.

6 Conclusion

The data showed that tACS group performed better than the sham group or the control group. And the results suggest that tACS induces plasticity and increase motor performance and adaptation.

6.1 Recommendation

tACS can be used in schizophrenia, depression and other physiatric disorders. It can be used in tumor regression and brain cortical connections can be sorted out using the technique of tACS. In Our study we tried to resolve the motor effect of tACS on right cerebellar tACS whereas two electrodes “active” can be used to stimulate both the cerebellar hemisphere together. Since purkinje fibers are present in both cerebellar hemispheres. Stimulation signal can be phase locked to the EEG signal correlating the natural oscillation.

7 References

Antal, A., & Herrmann, C. S. (2016). Transcranial Alternating Current and Random Noise Stimulation: Possible Mechanisms. *Neural Plasticity*. https://doi.org/10.1155/2016/3616807

Antal, A., & Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00317

Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Current Opinion in Neurobiology*, *15*(2), 161–167. https://doi.org/https://doi.org/10.1016/j.conb.2005.03.004

Fröhlich, F., & McCormick, D. A. (2010). Endogenous Electric Fields May Guide Neocortical Network Activity. *Neuron*, *67*(1), 129–143. https://doi.org/10.1016/j.neuron.2010.06.005

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience*, *7*, 279. https://doi.org/10.3389/fnhum.2013.00279

Mehta, A. R., Pogosyan, A., Brown, P., & Brittain, J.-S. (2015). Montage Matters: The Influence of Transcranial Alternating Current Stimulation on Human Physiological Tremor. *Brain Stimulation*, *8*(2), 260–268. https://doi.org/https://doi.org/10.1016/j.brs.2014.11.003

Molinari, M., Leggio, M. G., Filippini, V., Gioia, M. C., Cerasa, A., & Thaut, M. H. (2005). Sensorimotor transduction of time information is preserved in subjects with cerebellar damage. *Brain Research Bulletin*, *67*(6), 448–458. https://doi.org/https://doi.org/10.1016/j.brainresbull.2005.07.014

Nakazono, H., Ogata, K., Kuroda, T., & Tobimatsu, S. (2016). Phase and

Frequency-Dependent Effects of Transcranial Alternating Current Stimulation on Motor Cortical Excitability. *PloS One*, *11*(9), e0162521. https://doi.org/10.1371/journal.pone.0162521

Naro, A., Bramanti, A., Leo, A., Manuli, A., Sciarrone, F., Russo, M., … Calabro, R. S. (2017). Effects of cerebellar transcranial alternating current stimulation on motor cortex excitability and motor function. *Brain Structure & Function*, *222*(6), 2891–2906. https://doi.org/10.1007/s00429-016-1355-1

Naro, A., Leo, A., Russo, M., Cannavò, A., Milardi, D., Bramanti, P., & Calabrò, R. S. (2018). Does Transcranial Alternating Current Stimulation Induce Cerebellum Plasticity? Feasibility, Safety and Efficacy of a Novel Electrophysiological Approach. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *9*(3), 388–395. https://doi.org/10.1016/j.brs.2016.02.005

Naro, A., Milardi, D., Cacciola, A., Russo, M., Sciarrone, F., La Rosa, G., … Calabro, R. S. (2017). What Do We Know About the Influence of the Cerebellum on Walking Ability? Promising Findings from Transcranial Alternating Current Stimulation. *Cerebellum (London, England)*, *16*(4), 859–867. https://doi.org/10.1007/s12311-017-0859-4

Noah S. Philip, Brent G. Nelson, Flavio Frohlich, Kelvin O. Lim, Alik S. Widge, & Linda L. Carpenter. (2017). Low-Intensity Transcranial Current Stimulation in Psychiatry. *American Journal of Psychiatry*, *174*(7), 628–639. https://doi.org/10.1176/appi.ajp.2017.16090996

Paulus, W., Peterchev, A. V, & Ridding, M. (2013). Transcranial electric and magnetic stimulation: technique and paradigms. *Handbook of Clinical Neurology*, *116*, 329–342. https://doi.org/10.1016/B978-0-444-53497-2.00027-9

Reis, J., Prichard, G., & Fritsch, B. (2014). Chapter 8 - Motor System. In R. C.

Kadosh (Ed.), *The Stimulated Brain* (pp. 207–235). San Diego: Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-404704-4.00008-9

Repp, B. H. (2005). Sensorimotor synchronization: A review of the tapping literature. *Psychonomic Bulletin & Review*, *12*(6), 969–992. https://doi.org/10.3758/BF03206433

Richard S. Snell. (2010). *Clinical Neuroanatomy* (7th ed.). Wolters K Luwer (India) pvt ltd, New Delhi. Retrieved from http://thepoint.lww.com/snellneuro

Serrien, D. J. (2009). Interactions between new and pre-existing dynamics in bimanual movement control. *Experimental Brain Research*, *197*(3), 269–278. https://doi.org/10.1007/s00221-009-1910-6

Strüber, D., Rach, S., Neuling, T., & Herrmann, C. S. (2015). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. *Frontiers in Cellular Neuroscience*, *9*, 311. https://doi.org/10.3389/fncel.2015.00311

Vossen, A., Gross, J., & Thut, G. (2015). Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment. *Brain Stimulation*, *8*(3), 499–508. https://doi.org/https://doi.org/10.1016/j.brs.2014.12.004

Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., & Pollok, B. (2013). Effects of 10Hz and 20Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. *Behavioural Brain Research*, *241*, 1–6. https://doi.org/https://doi.org/10.1016/j.bbr.2012.11.038

Witt, S. T., Laird, A. R., & Meyerand, M. E. (2008). Functional neuroimaging correlates of finger-tapping task variations: An ALE meta-analysis. *NeuroImage*, *42*(1), 343–356.

https://doi.org/https://doi.org/10.1016/j.neuroimage.2008.04.025

Yavari, F., Jamil, A., Samani, M. M., Vidor, L. P., & Nitsche, M. A. (2018). Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction. *Neuroscience & Biobehavioral Reviews*, *85*, 81–92. https://doi.org/https://doi.org/10.1016/j.neubiorev.2017.06.015

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG. *PLOS ONE*, *5*(11), 1–7. https://doi.org/10.1371/journal.pone.0013766