Study of Selective Attention by Non-invasive Brain Stimulation

by

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Certificate

This is to certify that this masters' thesis entitled "**Study of Selective Attention by Non-invasive Brain Stimulation**" towards the partial fulfilment of the BS-MS dual degree programme at *Indian Institute of Science Education and Research, Pune*, is okay for submission and it represents original research carried out by **Sourav Mukherjee** at Indian Institute of Science, Bangalore under the supervision of **Dr. Sridharan Devarajan**, Assistant Professor, Centre for Neuroscience, IISc Bangalore during the academic year 2017-2018 .

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Contents

Abstract

Selectively attending to a subset of information coming is an integral process to navigate or to do any task in the real world. Endogenous neural oscillations play a role in selective attention. This project seeks to test the role of 40 Hz oscillatory non-invasive brain stimulation (tACS) and study the changes in the behaviour due to the stimulation. We quantified the effects of stimulation for changing the behaviour performance in attention tasks. We also discovered different effects upon stimulating different hemispheres of the brain. Our findings pave the way for using non-invasive brain stimulation strategies like tACS for treating clinical disorders like ADHD.

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Introduction

In the real world, one has to face a lot of different kinds of sensory inputs at the same time. Though many of the information received may not be important or relevant to the task at hand. So some sort of filtration is needed to perform properly. That is, one must focus on task relevant information while trying to minimize the interference from other task-irrelevant informations (Hanania and Smith, 2011; Carraco, 2011). This selective choice to attend to a fraction of the coming information is known as Selective Attention. This project aims to study the modulation of selective attention processes by external interferences like non-invasive brain stimulation techniques.

Neural oscillations

Neural oscillations are generated due to synchronous activity of a large number of neurons. In recent years, with the advent of different techniques like electroencephalography(EEG), magnetoencephalography(MEG), some more invasive techniques in animals ,and different behavioural task paradigms, it has been revealed that these oscillations play a role in dynamic cognitive processes like perception, attention, memory etc. (Başar et. al., 2001; Ward, 2003). There are five well established frequency bands- alpha: 8 - 13 Hz, theta: 3.5 - 7 Hz, delta: 0.5 - 3 Hz, gamma: 30 - 90 Hz and beta: 14 - 30 Hz (Başar et. al., 2001; Herrmann et. al., 2016; Buzsáki and Draguhn, 2004) and among these the gamma oscillation is of particular interest to us.

Gamma oscillations and its' role in attention

In the recent years, oscillatory activities in the gamma frequency band (30 - 90 Hz) has piqued a lot of interest, since it has been shown to have close association with various higher order cognitive processes for humans (Herrmann et. al., 2004; Kaiser and Lutzenberger, 2003; Tallon-Baudry and Bertrand, 1999). Though there are a lot of studies involving the biological processes underlying the gamma oscillation (Gray, 1994; Whittington et. al., 2000; Bartos et. al., 2007; Tiesinga and Sejnowski, 2009; Wang,

2010), the exact functions and mechanisms are a matter of doubt (Buzsáki and Wang, 2012; Ray and Maunsell, 2015). But mostly from theoretical frameworks as well as from experimental studies, gamma oscillations are closely linked with the activity of inhibitory interneurons (Buzsáki and Wang, 2012; Whittington et. al., 2000) of the brain. Gamma oscillations are important to us as it has been shown that selective attention can modulate gamma power (Fries et. al., 2001). Directing one's attention towards a particular location generally increases the amplitude of gamma oscillations and also, in the neocortical areas where the particular stimulus is encoded, the synchronization of spikes to these gamma oscillations increases (Fries et. al., 2001; Gregoriou et.al., 2009; Sridharan and Knudsen, 2015). Along with these findings, the close association of different neuro-psychiatric disorders with alterations of gamma oscillations is also notable. Patients with Attention- deficit Hyperactivity disorder (ADHD) show a significant increase in gamma amplitude (Herrmann and Demiralp, 2005; Yordanova et. al., 2001). These evidences indicate towards a strong relation between gamma band oscillation and attention.

Modulation of neural oscillations: Transcranial electrical stimulations

As we have seen so far, neural oscillations have a pretty close association with the cognitive processes. These oscillations have been recorded from humans as well as animals during various different task paradigms and behavioural states. But the key point is, most of these studies have established correlation between the oscillatory brain activities and the cognitive processes. Whether this correlation leads to causation, that is still unclear at this point. To elaborate, we are not still sure about whether these oscillations represent some fundamental mechanism or it is just an epiphenomenon of cognitive functions (Herrmann et. al., 2013). So it has been argued that modulating the brain oscillations might potentially alter the cognitive processes, even further down the line, it might also help in clinical cases by treating a lot of neurological disorders (Reato et. al., 2013; Kobayashi and Pascual-Leone, 2003; Gandiga et. al., 2006). In this regard, alternating current stimulation techniques might be useful since it can target specific

endogenous brain oscillations associated with different cognitive processes (Antal et. al., 2008; Antal and Paulus, 2013). A number of human studies have also shown that time-varying current stimulations can influence cortical excitability (Marshall et. al., 2006; Antal et. al., 2008; Kirov et. al., 2009). It has also been shown that like constant current application (DC), alternating current can also modulate the membrane potential of a large number of neurons at the stimulation site. In this current study tACS (Transcranial Alternating Current Stimulation) with sinusoidal current amplitudes has been used.

Mechanism of tACS

There have been a few studies on animals with intracranial recordings that give us insights on possible physiological mechanism of tACS (Fröhlich and Mccormick, 2010). It has been revealed through in-vivo recordings that the spiking activity is synchronized to driving frequencies which indicates a possible entrainment of neural activity to electrically applied field. This study by Fröhlich and Mccormick also show that in addition to the absolute voltage levels applied, the temporal dynamics of voltage change is also important in determining the neural activity. Some effects might be different with parameters like the site of stimulation, skull thickness etc. Current intensity and phase of the stimulation may also be important. A study on humans has shown that the cortical excitability depends non-linearly with the current intensity (Moliadze et. al., 2012). It goes on to reveal that inhibitory neurons are more susceptible to stimulation and can be stimulated at lower intensities whereas, excitatory neurons have a higher threshold and can only be stimulated at a higher current intensity. tACS also has a role to play in modulating large cortical network. It has been shown to have more impact in network resonance than direct current stimulation (Ali et. al., 2013). Apart from the neuro physiological evidences, behaviour modulation in different task paradigms has also been studied through cortical entrainment using tACS (Herrmann et. al. 2013; Tavakoli and Yun, 2017).

Mechanisms of attention

A lot of studies investigating attention employ different kinds of signal detection tasks at multiple locations. Attention at a particular location can enhance performance at that location by either increasing sensitivity, that is increasing the quality of the stimulus perceived or by modulating bias, that is giving differential weightage during decision making. When we study attention, we basically study how these measures- sensitivity and bias are being modulated.

Aim and scope of the project

The broad aim of the project is to study selective attention and how can we modulate attention using non invasive brain stimulations like tACS. We have known from the existing literature about the role of gamma oscillations in attention and how attentional task can modulate gamma amplitude. Also we know from other modalities, brain regions like PPC (Posterior parietal cortex) are heavily involved in attention (Malhotra et. al., 2009; Moore et. al., 2003). So, the main goal is to stimulate PPC at gamma frequency and to study how the behaviour is altered in an attention task paradigm. In addition to confirming the role of neural oscillations in higher order cognitive processes, this work might shed light on whether these oscillations have a causal link to these processes. We also stimulate PPC from both left and right hemispheres separately. These data might indicate the differences in attentional networks in the two hemispheres and also if one is dominant over another during attention.

Materials and methods

We have run a total of 24 subjects with 16 subjects in one protocol and 8 subjects in a slightly different protocol. All the subjects have voluntarily given their consent for running the experiment on them and for doing a brain stimulation. All the experiments were carried out in the Cognition lab, Indian Institute of Science in accordance to the ethical committee of IISc. The subjects are stimulated in both left and right PPC(posterior parietal cortex) by transcranial alternating current while doing a behavioural task. Performance in the behavioural task is assessed to remark on the effects of the stimulation. The different parts of the experimental and analytic procedure is described separately here.

Brain stimulation

Alternating current stimulation is an integral part of the experiment. For stimulation purposes, we use a *1 x 1 low intensity transcranial electrical stimulator* (provided by Soterix medical, model : 2001). We also use *4 x 1 multichannel stimulation interface* (Soterix medical) to divide the current into multiple electrodes. For the experiments, in total 5 electrodes are used, in which one electrode is the central or the main electrode and the other four electrodes are reference electrodes. The kit comes with a specialized tES cap and holders. During the whole experimental procedures these holders keep the electrodes at the designated position.

The stimulator gives us the option to choose from different waveforms for the applied current. Since we are interested in Alternating Current stimulation, we used sinusoidal waveform. There are other options like frequency, polarity of the current, maximum current intensity, duration of the stimulation etc. which allow us to control these parameters according to our task requirements. There were two cohorts run with two protocols. In the first protocol, 16 subjects were run with 40 Hz frequency and 0.75 mA maximum current intensity, whereas in the second protocol, we ran 8 subjects with 40

Hz frequency but with maximum current intensity 1 mA. The other parameters were kept same as before. There was also a modification in the task setting. That will be discussed later on.

Fig. 1: A 1 x 1 low intensity transcranial Electrical Stimulator has been used for Alternating current Stimulation (COPYRIGHT: Soterix Medical)

Task Design

We employ a 2-ADC (2 - Alternative detection/ change detection) task to model the behaviour and to observe alterations due to brain stimulation. In a 2-ADC task, we present a fixation cross at the center of the screen (subject sits approximately 60cm away from the screen). The subject has to fixate on the cross for the whole experiment. After a certain time, a cue appears just above the fixation cross pointing either towards left or right. The subject is asked to attend towards the cued side. After a variable amount of time, two gabor patches appear on either side of the fixation cross with certain orientation. Then after a blanc screen for certain period, the gabor patches reappear with either one of them may or may not change its' orientation. The subject has to respond, whether he or she has perceived a change on the left gabor or a change on the right gabor or hasn't perceived any change at all. The subject responds using a 8-key cedrus box.

Depending on the cue and the actual change happening, there can be three types of trials. First, where the change occurs on the same side, where the cue was pointing at. These are called *Valid trials*. Second, where the change occurs on the opposite side of where the cue was pointing at. These are called *Invalid trials*. And lastly, the trials with no change in orientation. They are called *No-change trials* or *Catch trials*. In a block of 50 trials, the ratio of valid, invalid and no-change trials are- 30 : 10 : 10.

Detecting the change in orientation is a kind of target feature detection task where we can vary the 'strength' of the target feature, in this case the change in angle and see how the performance vary. We basically have 5 angle changes for both the valid and invalid trials. In the first cohort of 16 subjects, the change in angles were- 5, 9, 15, 26 and 45. And in the second cohort of 8 subjects, the changes in angles were- 5, 15, 45, 65 and 90. All the angles are in degrees. This modification was made to see whether and how the performance saturates over large changes in orientation.

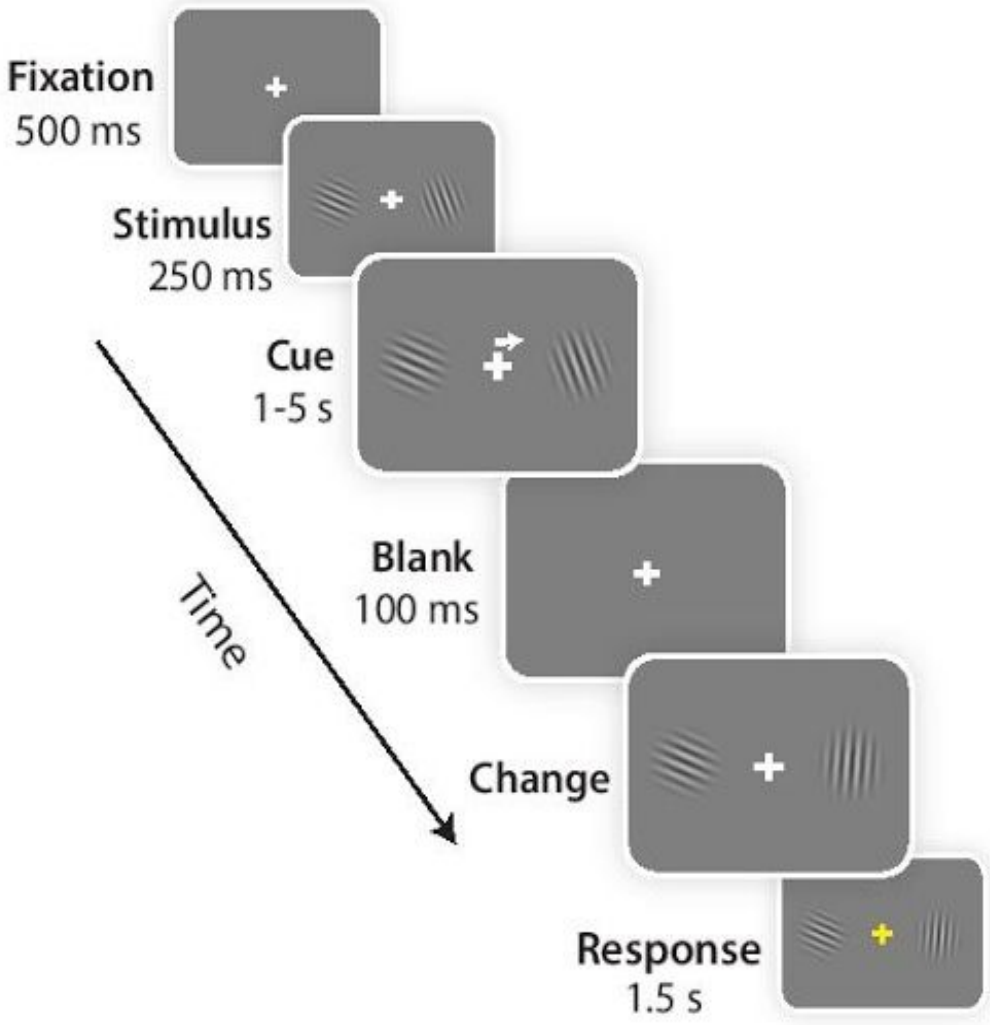


Fig. 2: A schematic diagram showing a 2-ADC task paradigm. This figure shows the timeline events for a Single trial. The task is coded in psychtoolbox, a utility of MATLAB for psychophysical experiments

Experimental procedure

As stated earlier, the 2-ADC task paradigm is employed to study the behaviour. A typical experiment spans approximately a week and a half. On the first day, the subject is trained on the 2-ADC task while we also take their eye-tracking data. The subject is asked to do typically 5-7 blocks, where each block contains 50 trials in continuum. Feedback on the quality of fixation might be given to the subject depending on the data. The training session may also stands as a selective stage as subjects with very bad eye-tracking data are not carried on for the next sessions. After a successful training, the first stimulation is done within 2~3 days. A stimulation day experiment consists of 15 blocks, with 50 trials in each block. The whole period is again divided into 3 sessions of 5 blocks each. The first session is called sham session. The applied stimulation current is ramped up and immediately brought down in this session. It's basically acts as a control since the only sensation of being stimulated is when the current ramps up. The second session is called stim session. Here, the subject is actually being stimulated on either of his hemisphere for ~20 minutes. And the third session is called post, where there is no stimulation applied. There is a gap of 30 minutes between second and third session. Post session is used to observe whether the stimulation-induced effects are washed out or not. A similar stimulation day is carried out at least 6-7 days apart (from the first stimulation day) on the other hemisphere.

Modelling behaviour

Our main goal is to study selective attention through this 2-ADC task framework. According to the responses and actual change occured or no change, we can create a contingency table where we can sum up the results in the following format-

Hit: When the subject correctly responded a left change or a right change

False Alarm: When there is actually no change, but a subject responded either a left change or a right change

Misidentification: When there is actually a left change but the subject responded right change and vice versa

Miss: When there is actually a change in either left or right side but the subject responded no change

Correct Rejection: When a subject correctly responded a no-change trial

	Left change response	**Right change response**	**No-change response**
Left side changed	Hit	Misidentification	Miss
Right side changed	Misidentification	Hit	Miss
No change	False alarm	False alarm	Correct rejection

Table. 1: A contingency table for 2-ADC task setting

A contingency table like this is computed for each angle change . We also get a similar contingency table of probabilities for each of these category by dividing the respective counts with the total number of trials. Each row in this contingency tables sums up to be 1.

These hit rates and false alarm rates are used to compute parameters like sensitivity (denoted by d') and criterion (c) by a computational model named m-ADC model (Sridharan et. al., 2014). It is based on signal detection theoretic framework and gives us the parametric values by optimization. These computed d' and c values are used further to compute different bias measures like constant criterion. We tried to look for stimulation effects in these computed parameters.

Results and Discussion

In the first cohort, we ran 16 subjects with 40 Hz stimulation frequency and 0.75 mA alternating current. The results are shown below-

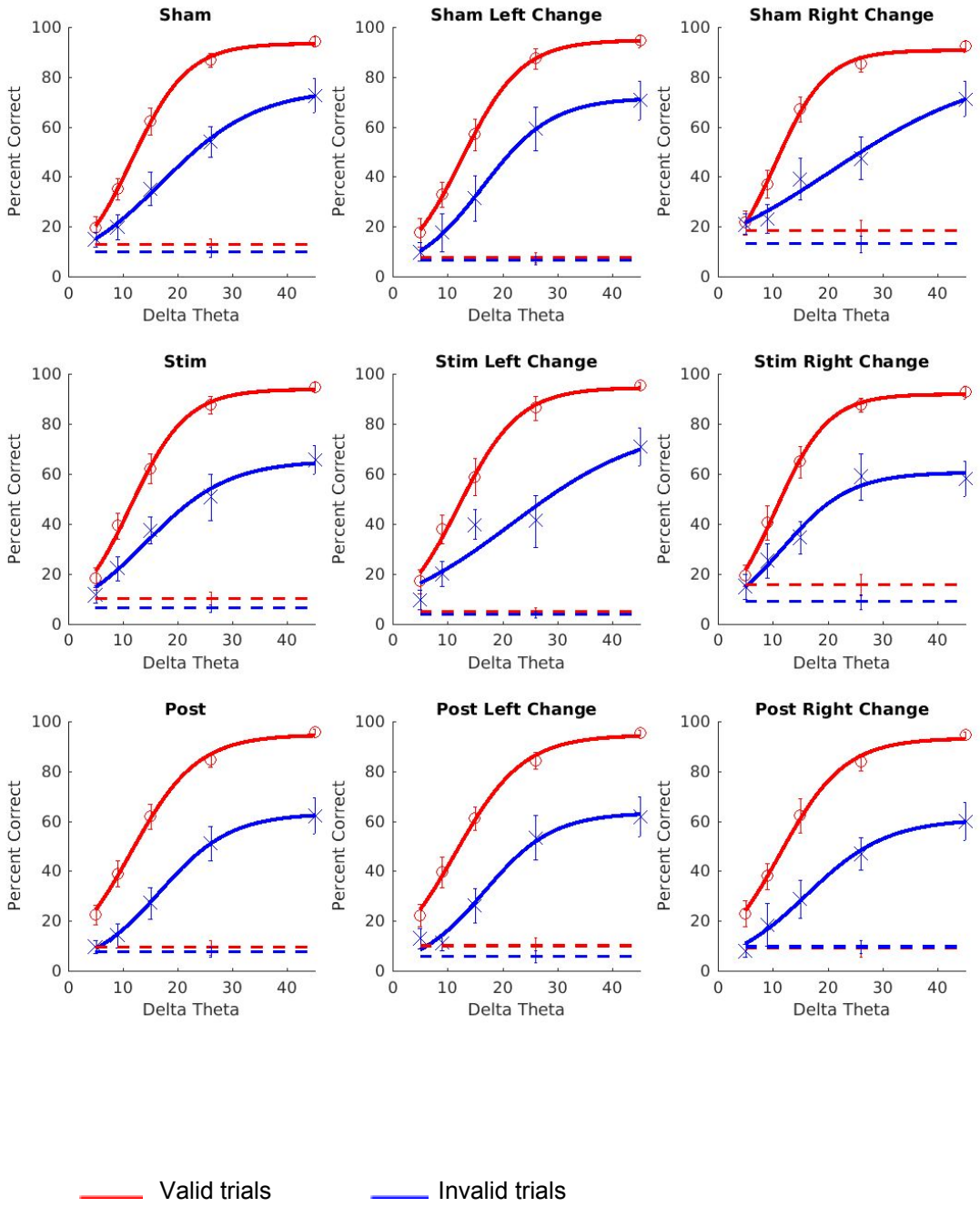


Fig. 3 Left hemisphere stimulation: psychometric curve (accuracy or percent correct vs the change in angle). The rows indicate different sessions- sham, stim, post and the columns represent overall data, left side changed data and right side changed data respectively. The dotted lines represent false alarm rates

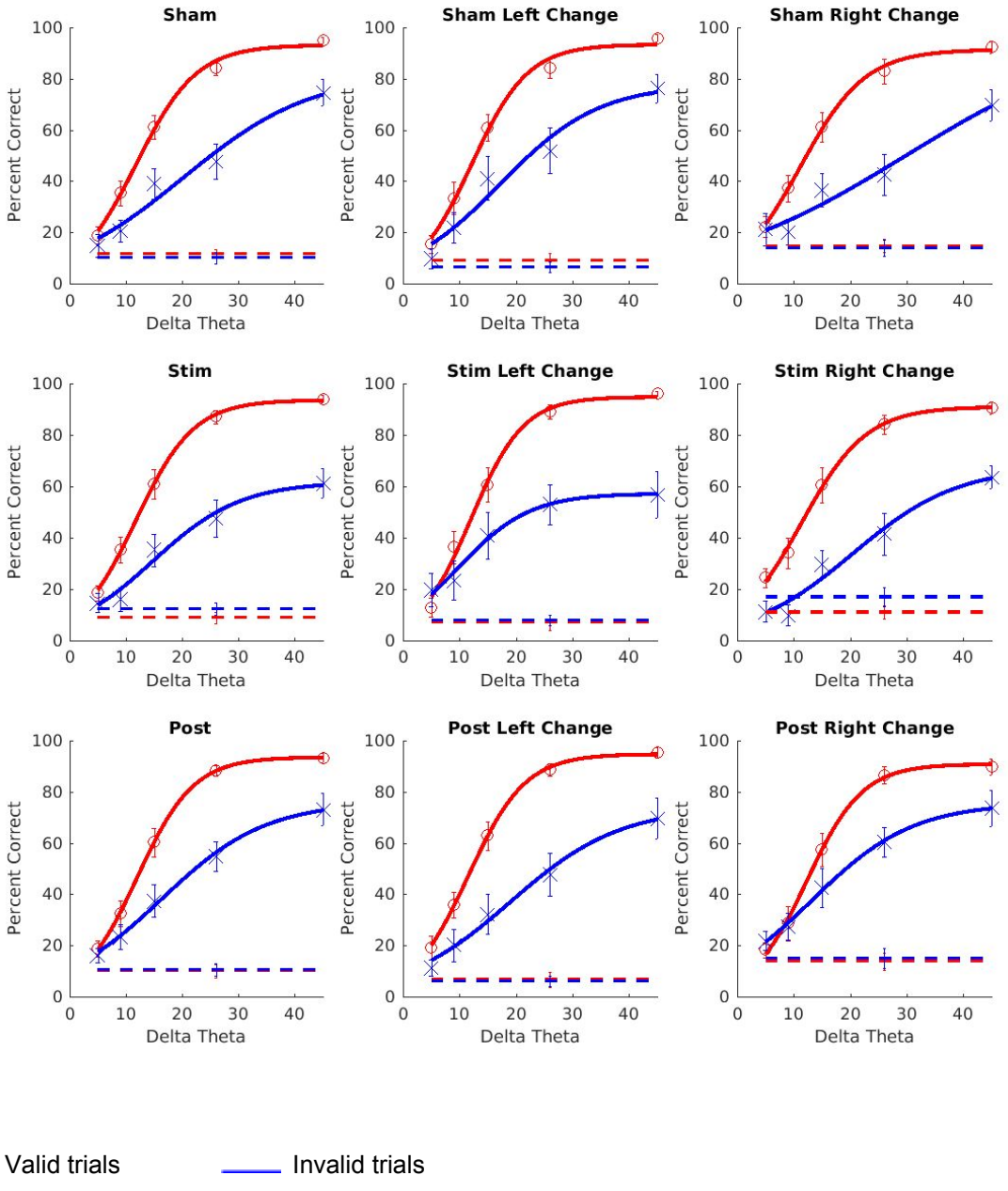


Fig. 4: Right hemisphere stimulation: psychometric graph. As earlier, the rows represent the sessions- sham, stim and post whereas the columns represent overall data, left change data and right change data. The dotted lines represent false alarm rates

These two plots here are pooled plots for all the 16 subjects of first cohort. A pooled analysis is basically done by adding up all the contingency tables into one and treat the resultant contingency table as a single subject and do the required analysis as done for individual subjects. The error bars here are jackknife error bars. These psychometric plots are raw data in the sense they reflect the performance of the subject directly. Afterwards, we pass this data through the madc model to compute our parameters for interest.

For left hemisphere stimulation in the first cohort, we see

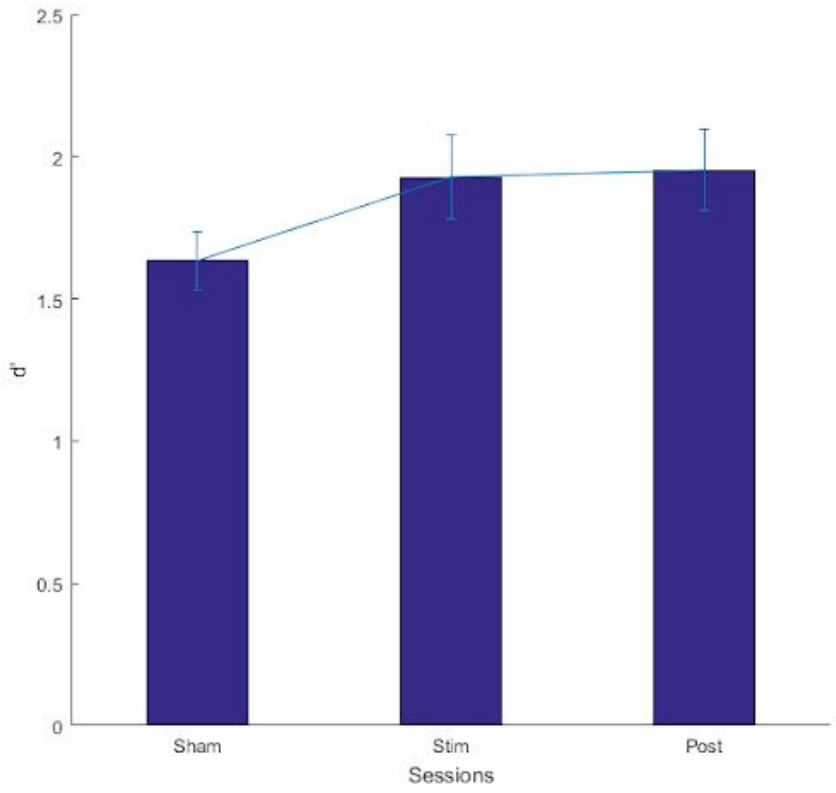


Fig. 5a: Left hemisphere stimulation, a psyphysical plot for only valid trials. The x- axis represents the sessions while the y-axis represent sensitivity or d' value

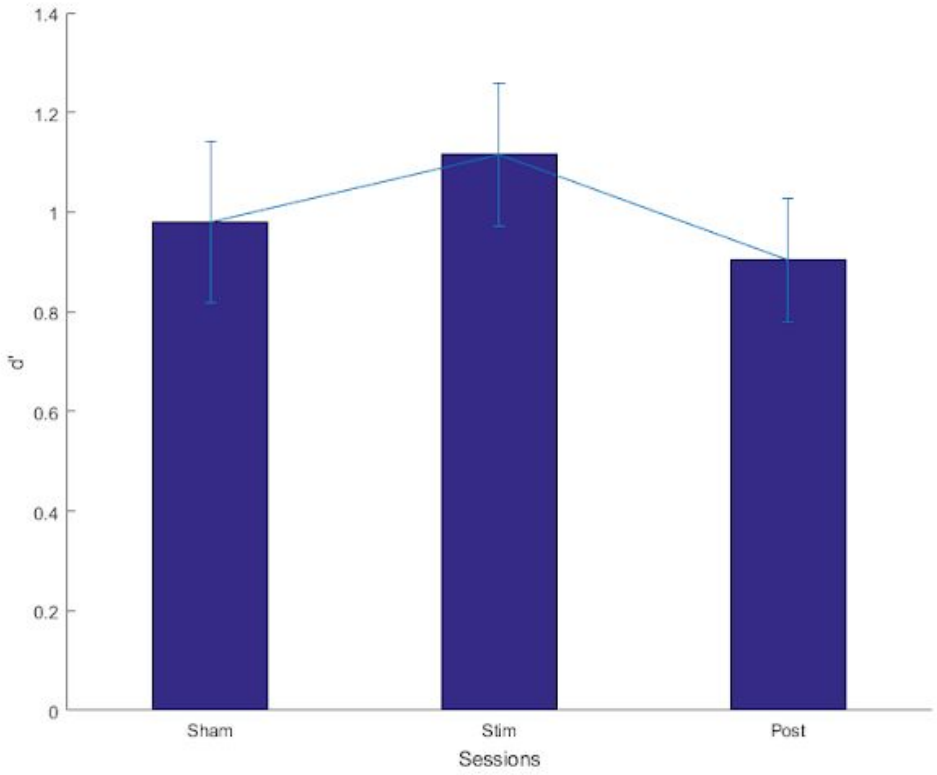


Fig. 5b: Left hemisphere stimulation, a psyphysical plot for invalid trials. The x- axis represents the sessions while the y-axis represent sensitivity or d' value

In these two plots above, we observe sensitivity (d') across the three sessions. These d' values are averaged across all the angles and then for all 16 subjects. From these results, we see that for the left hemisphere stimulation, if we look at the valid trials, there is a significant increase of d' value (*p- value 0.0299*) from sham to stim session. Though there is also a significant difference in sham to post session (*p- value 0.0151*). But on the other hand, for invalid trials, we see no significant difference (*p-value 0.3794*).

Similarly for the Right hemisphere stimulation in the first cohort (16 subjects)-

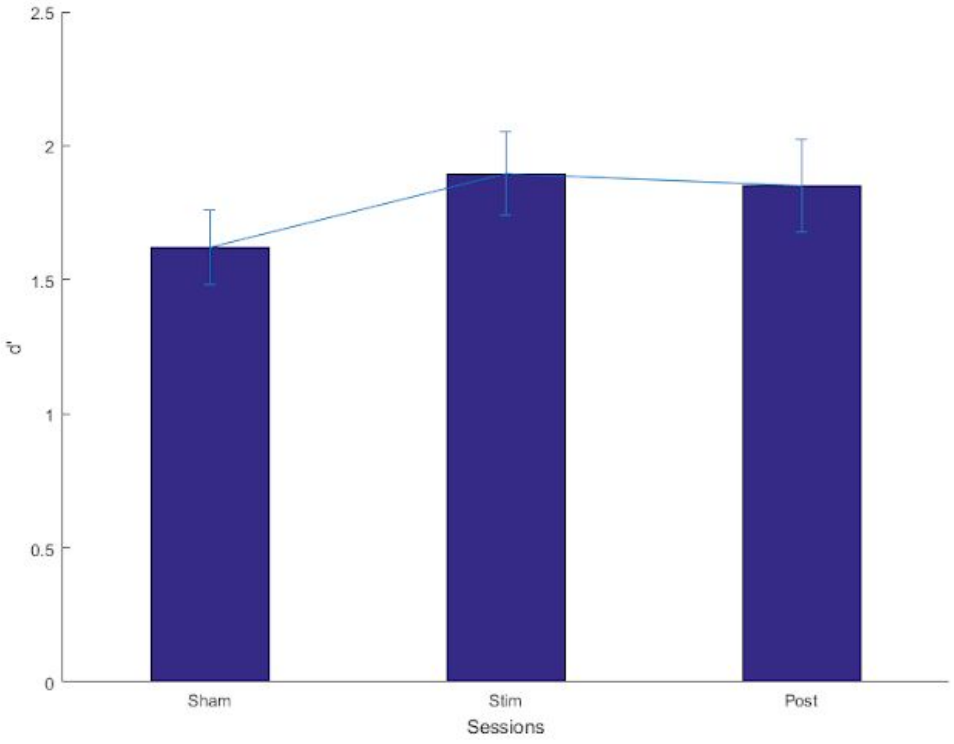


Fig. 6a: Right hemisphere stimulation, a psyphysical plot for only valid trials. The x- axis represents the sessions while the y-axis represent sensitivity or d' value

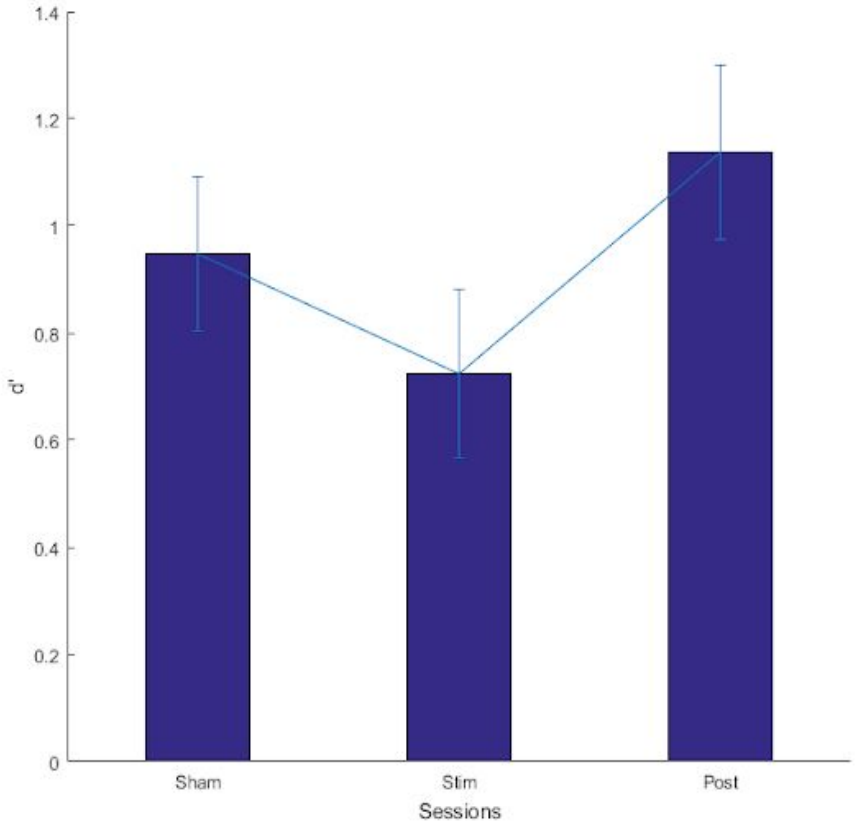


Fig. 6b: Right hemisphere stimulation, a psyphysical plot for the invalid trials. The x- axis represents the sessions while the y-axis represent sensitivity or d' value

For the right hemisphere, the stimulation effects doesn't seem to be significant. For valid trials only, though there is an increasing trend from sham to stim session, the effect is not significant (p- value 0.0787). For invalid trials, there is no significant effect.

Now we observe the effect of stimulation on bias. We use lr bias which is a measure of bias and is computed using sensitivity values of all the angles and the criterion value. For left hemisphere stimulation-

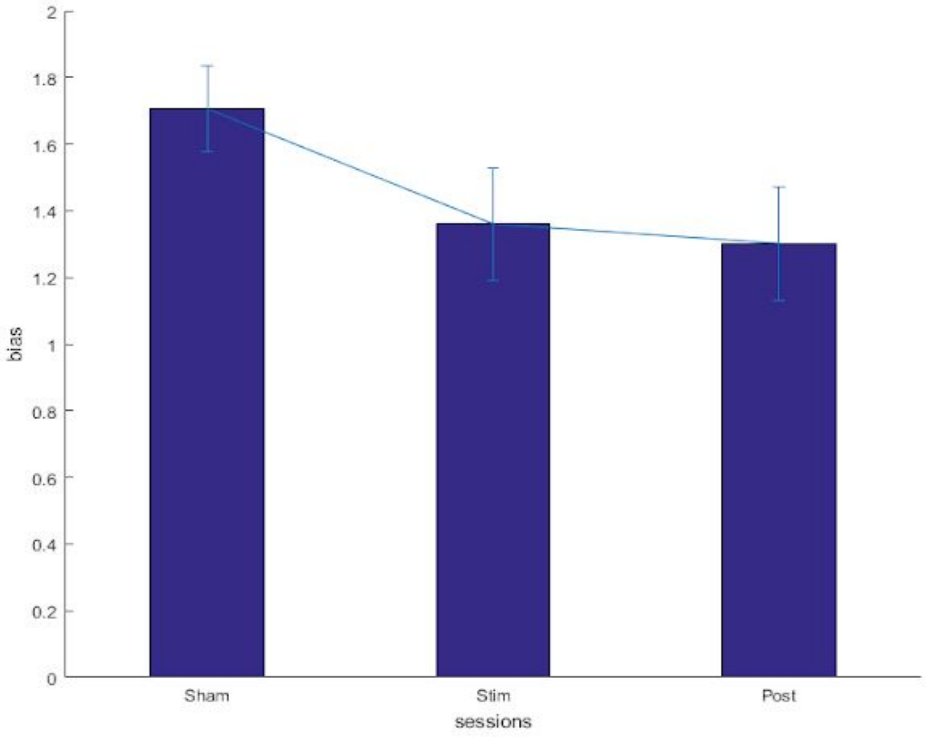


Fig. 7: Left hemisphere stimulation; on the x-axis we have sessions and in the y- axis we have lr bias values. Averaged over all the trials

As we can see, if we averaged over all the trials, for left hemisphere stimulation, there is a significant decrease in bias value from sham session to stim session (*p- value 0.0174*) and this does not revert back in the post session as sham to post values are also significantly different (*p- value 0.0229*).

Further, analysing the trials by valid and invalid trials, we can see that for the valid trials the effects is not significant from sham to stim (*p- value 0.1089*) but the bias decreases significantly for invalid trials (*p- value 0.0151*).

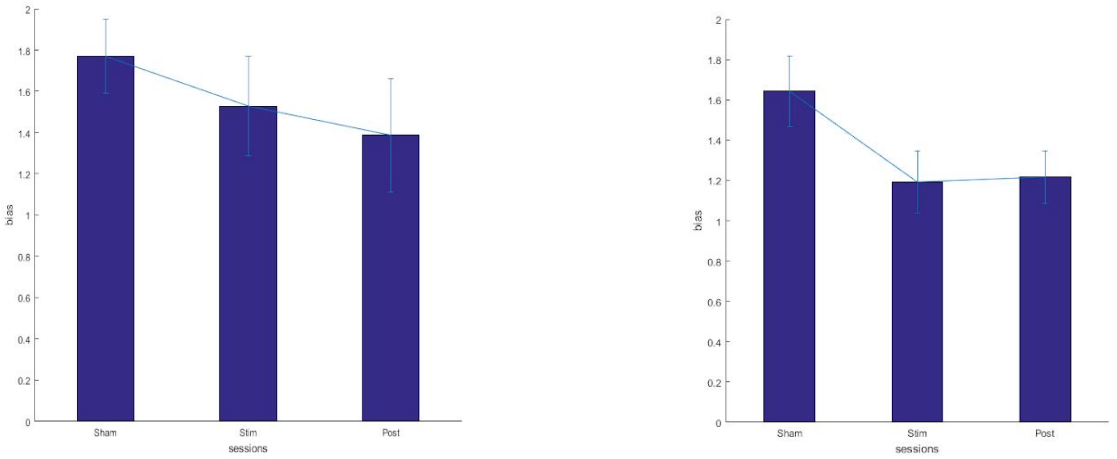
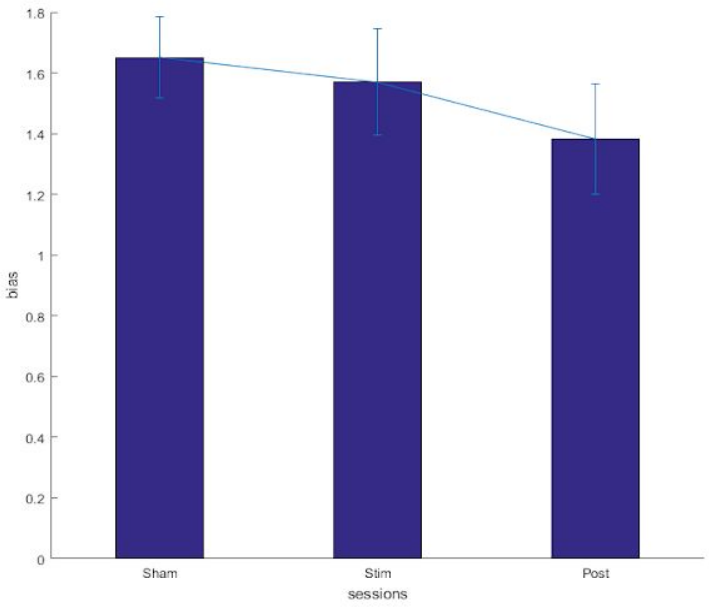
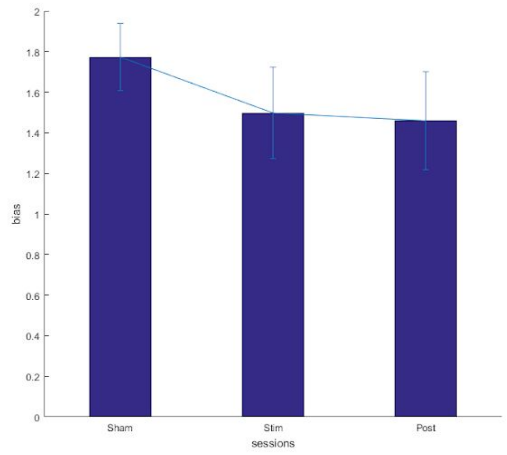


Fig. 8. **a:** Left hemisphere stimulation; bias vs sessions for valid trials. **b:** Left hemisphere stimulation; bias vs sessions for invalid trials

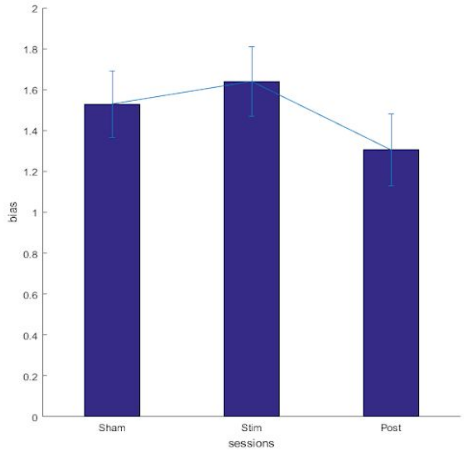
But for right hemisphere stimulation, we see no significant effect on bias. When averaged over all the trials, sham to stim session is not significantly different (p- value 0.6791). Analyzing the trials into valid and invalid shows no significant effect in either of those.



a



b

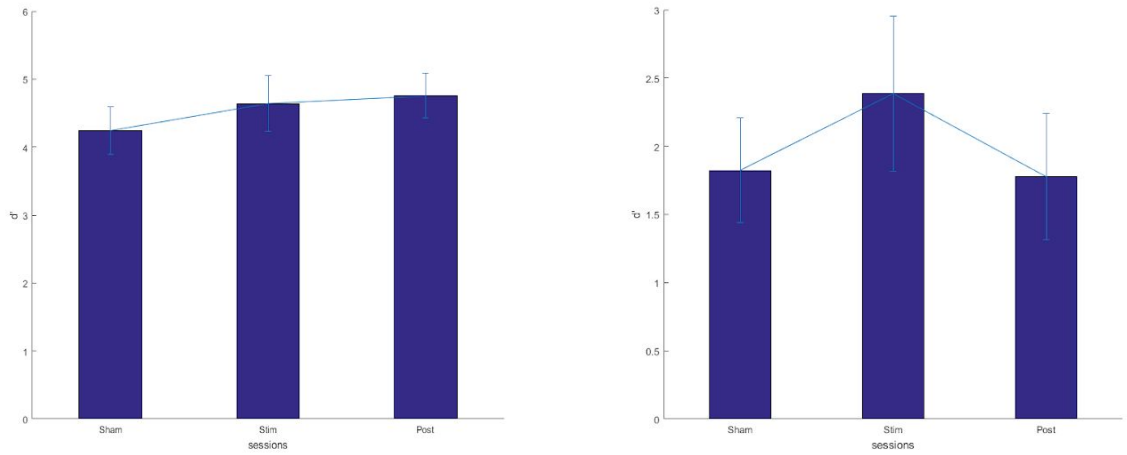


c

Fig. 9: Right hemisphere stimulation effect on bias; **a**: overall trials. **b**: valid trials. **c**: invalid trials

Next, we have increased the stimulation current intensity from 0.75 mA to 1 mA and ran an 8 subject cohort. In this cohort, we also changed the angle set for orientation change.

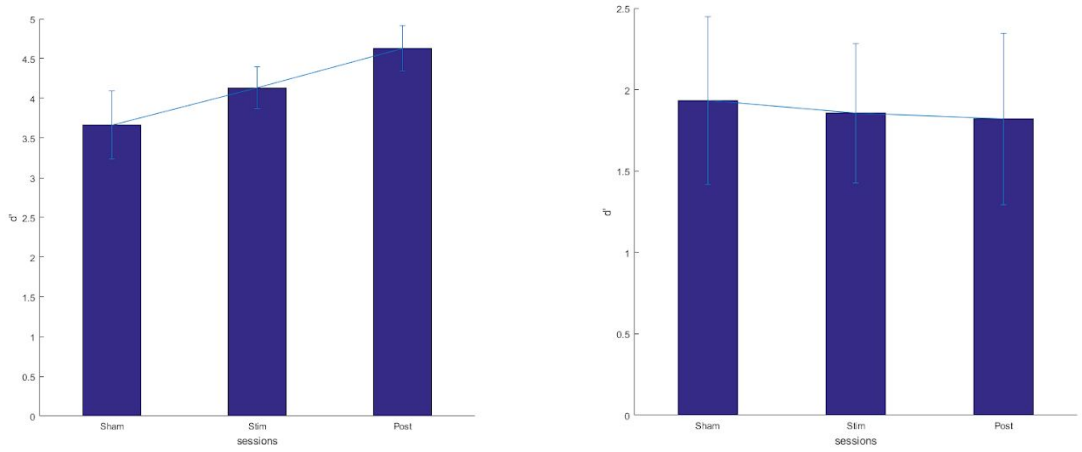
In this cohort, for left hemisphere stimulation we observe that though the trend is similar, that is an increase from sham to stim session, the effect is not significant. Especially, for the invalid trials, we see a clear increasing trend from sham to stim. This effect might become significant if we increase the number of subjects.



a **b**

Fig.10: Effect of Left hemisphere stimulation on sensitivity for the second cohort. **a**: valid trials **b**: invalid trials

For right hemisphere stimulation also, we see that the stimulation has no significant effect either on valid (sham to stim, *p- value 0.25*) or in the invalid trials (*p- value 0.8434*).



a b

Fig.11: Effect of Right hemisphere stimulation on sensitivity for the second cohort. **a**: valid trials **b**: invalid trials

For bias measure, we did similar analysis like the previous cohort. For left hemisphere stimulation, we see no significant difference in bias value from sham to stim.

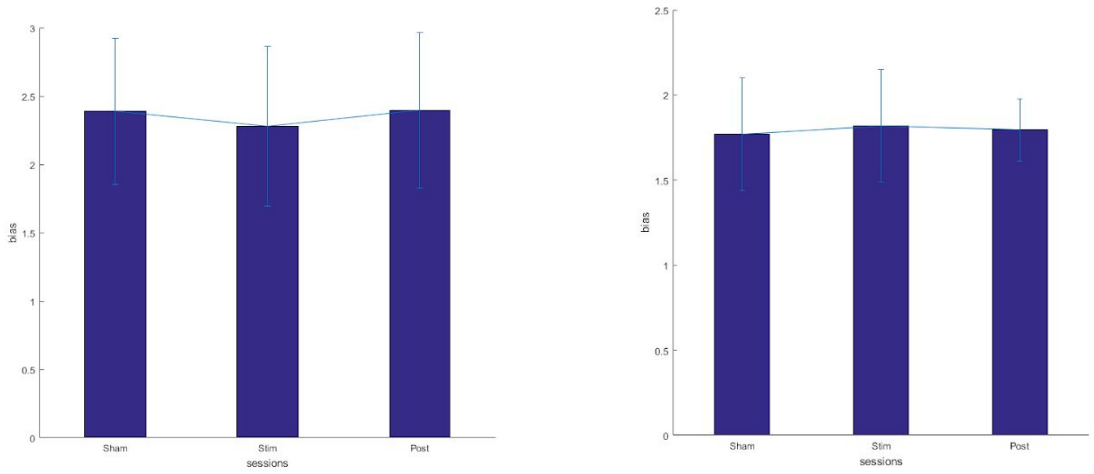


Fig.12 : Effect of Left hemisphere stimulation on bias for the second cohort. **a**: valid trials **b**: invalid trials

But, for right hemisphere stimulation, we find a significant increase in bias value from sham to stim session (*p- value 0.0234*)

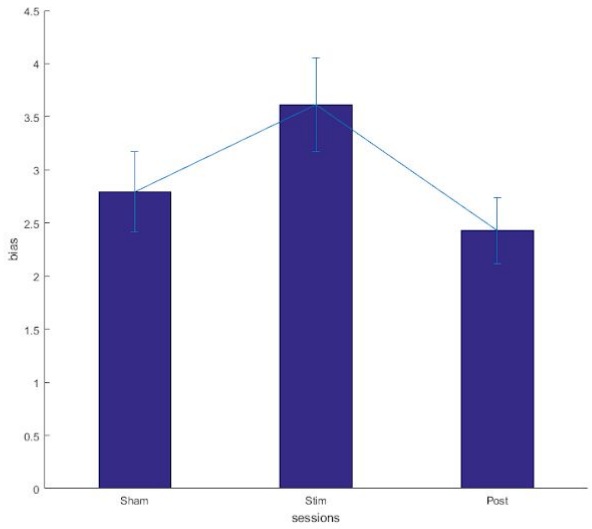


Fig. 13: Effect of Right hemisphere stimulation on bias for the second cohort

As we see from the results, most of the trends are consistent over the two cohorts; in some cases the effects being amplified like effect of right hemisphere stimulation on bias. Since the frequency of the applied stimulating current was same (40 Hz), this is somewhat expected.

Since we have similar trends, for further analysis, we combine both the cohorts and do analysis on a total of 24 subjects.

We do a N-way ANOVA test on the 24subject data. For left hemisphere stimulation, though we see that the main effect is not significant (p-value 0.0853), what is interesting is we see an interaction effect for stimulation and the side that is changed.

Analysis of Variance

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
session1	2.52	1	2.516	3.05	0.0853
change	4.9	1	4.897	6.14	0.0155
validity	18.39	1	18.385	10.91	0.0021
angles	646.02	1	646.024	144.52	0
sub	38.06	23	1.655	0.82	0.6892
session1*change	2.39	1	2.39	4.13	0.0424
session1*validity	0.08	1	0.084	0.15	0.7026
session1*angles	0.38	1	0.384	0.66	0.4157
session1*sub	28.43	23	1.236	2.14	0.0015
change*validity	2.57	1	2.574	4.45	0.0352
change*angles	5.74	1	5.739	9.92	0.0017
change*sub	26.7	23	1.161	2.01	0.0035
validity*angles	27.23	1	27.229	47.06	0
validity*sub	80.98	23	3.521	6.09	0
angles*sub	158.02	23	6.871	11.88	0
Error	482.52	834	0.579		
Total	1803.45	959			

Table.2 : Anova table for left hemisphere stimulation on sensitivity

But again, Anova test assumes that the data is from a Normal distribution. That is an assumption that we do not know. So it would be better to run a nonparametric test like bootstrapping on the data, where we basically randomly change the label of the data of

sham and stim session and then do all the analysis and check (stim - sham) metric to see if the difference is above chance or not and with how much significant difference is. Here we tabulate all the significant results from bootstrap analysis for all the trials on all 24 subjects

	d’	cc bias	lr bias
valid	sham < stim (p value 0.03)	-	-
invalid	sham < stim (p value 0.01)	sham < stim (p value < 0.001)	sham > stim (p value <0.001)
(valid- invalid)	-	sham > stim (p value 0.01)	-

Table.3: Overall bootstrap analysis data for left hemisphere stimulation

	d’	cc bias	lr bias
valid	-	-	-
invalid	-	sham < stim (p value 0.01)	-
(valid- invalid)	-	sham > stim (p value 0.03)	-

Table.4: Overall bootstrap analysis data for right hemisphere stimulation

The bootstrap analysis results show a definite increase in sensitivity. Additionally we see, left hemisphere stimulation increases sensitivity ipsilaterally for both valid trials (*p- value 0.01*) and invalid trials (*p- value 0.02*). For Right hemisphere stimulation, sensitivity increased contralaterally (*p- value 0.02*) for the valid trials. In case of bias, we see that lr bias decreases significantly for the invalid trials for left hemisphere stimulation whereas right hemisphere stimulation does not have a significant effect.

So, in conclusion we see some effect of modulation by tACS in our study. What is also very promising is that some of the results from a parallel cTBS study in the lab, which stimulates right hemisphere PPC are consistent with our study.

An issue with the results is the performance in the post session does not revert back to the baseline performance as we would have liked. A possible explanation might be that the wash out time that we give after stimulation (30 min) is not enough. So the tACS- induced effects are still seen in the post session. It also might be the case that the effects that we are observing are due to the subject being more familiar with the task as they go into the later blocks of trials. It might have been helpful if we can randomly do the first session but the task setup also does not allow us to randomize the sham and stim session.

That's why another small cohort is being run currently with random noise stimulation. This is just a control test and 4 people have been stimulated with random noise stimulation in both left and right PPC presently. Initial results show-

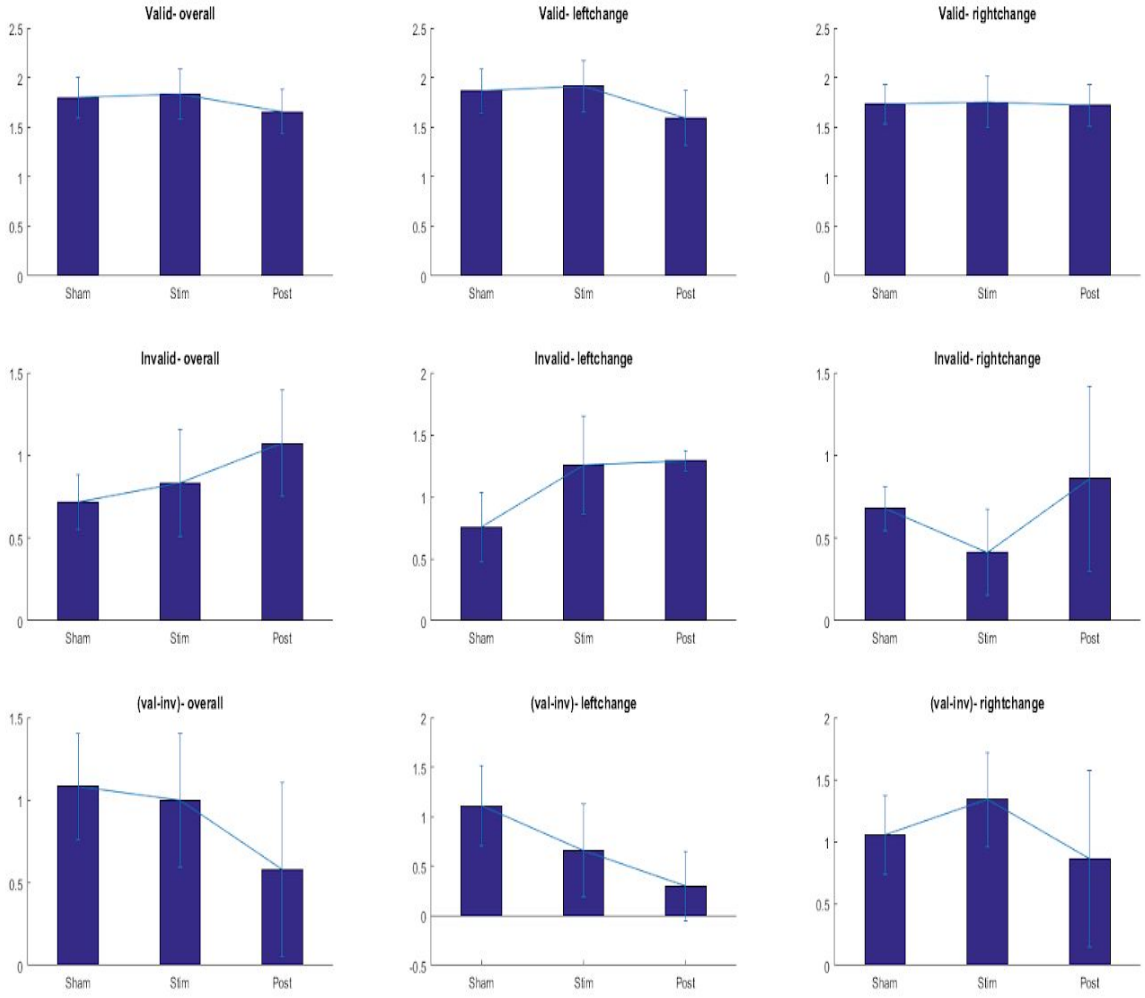


Fig. 14: Effect of left hemisphere random noise stimulation on sensitivity. The rows indicate valid, invalid and (valid- invalid) data, whereas the columns represent overall trials, left side changed trials and right side changed trials.

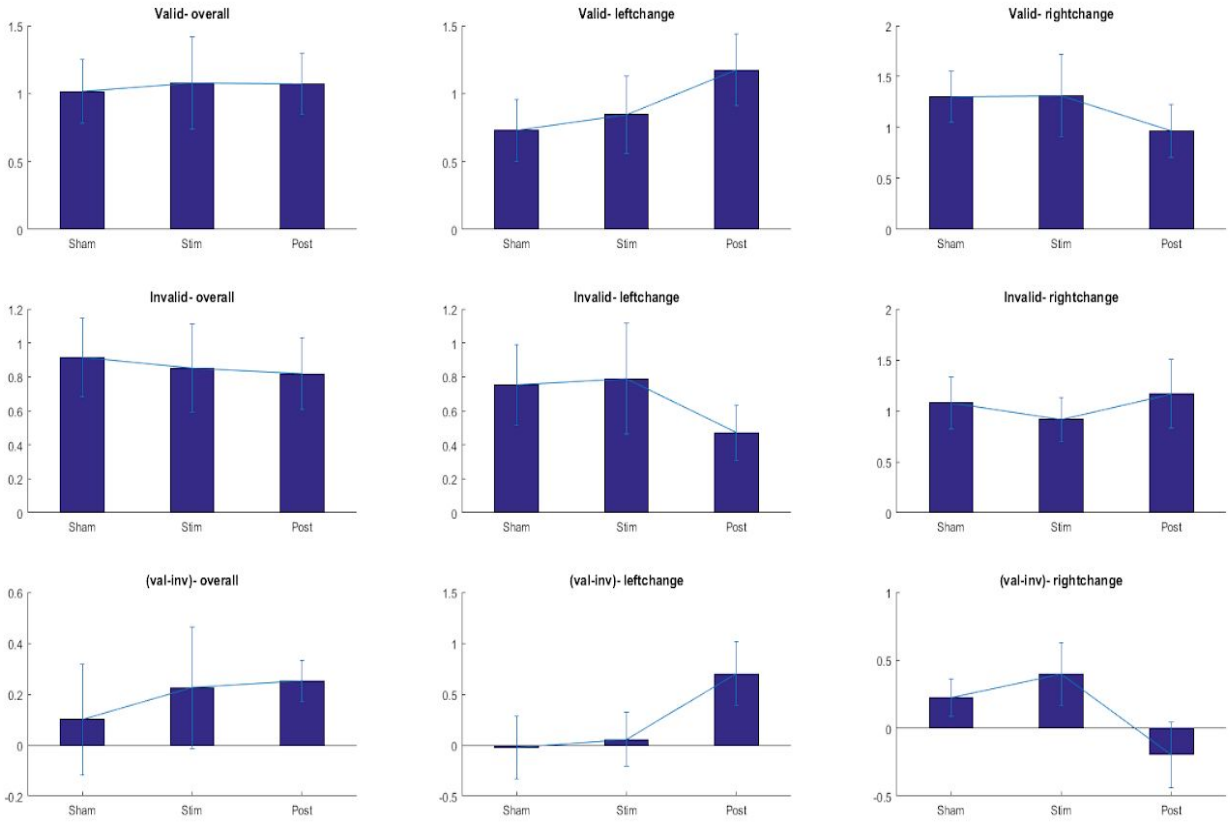


Fig. 15: Effect of left hemisphere random noise stimulation on bias. The rows indicate valid, invalid and (valid- invalid) data, whereas the columns represent overall trials, left side changed trials and right side changed trials.

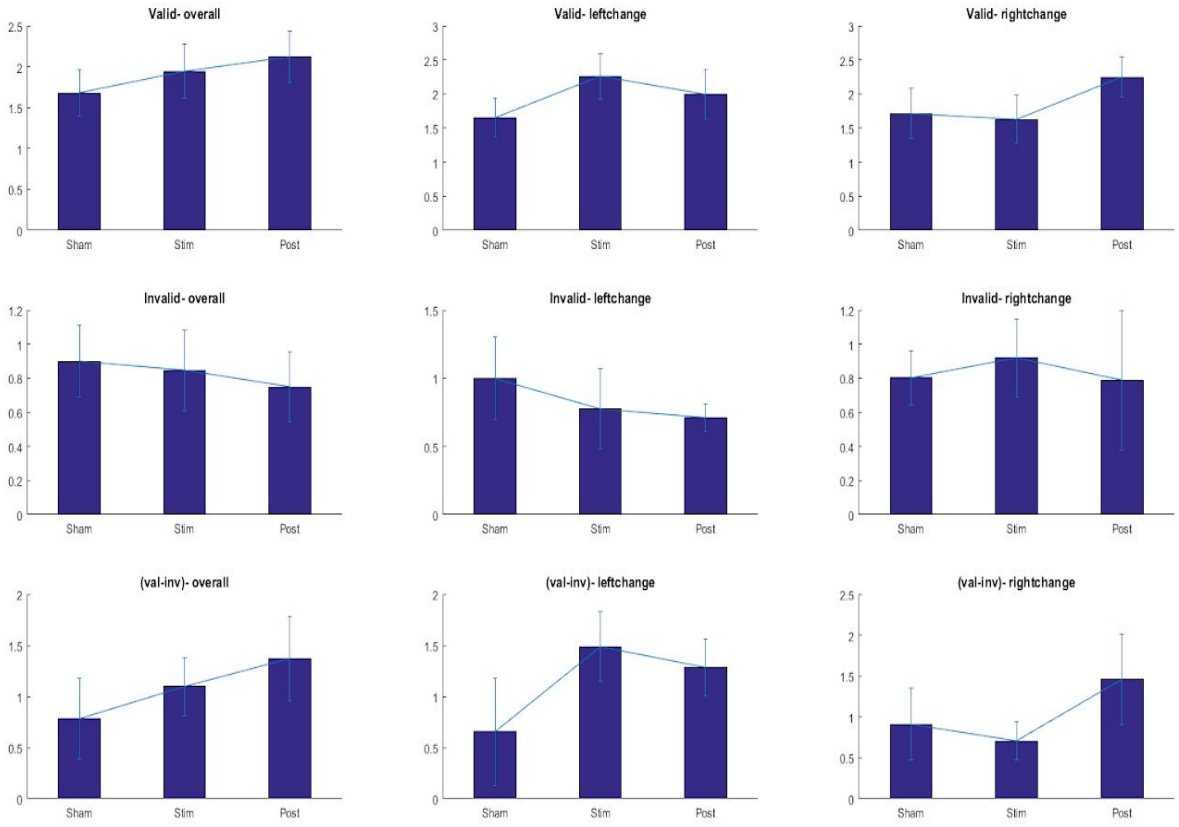


Fig. 16: Effect of right hemisphere random noise stimulation on sensitivity. The rows indicate valid, invalid and (valid- invalid) data, whereas the columns represent overall trials, left side changed trials and right side changed trials.

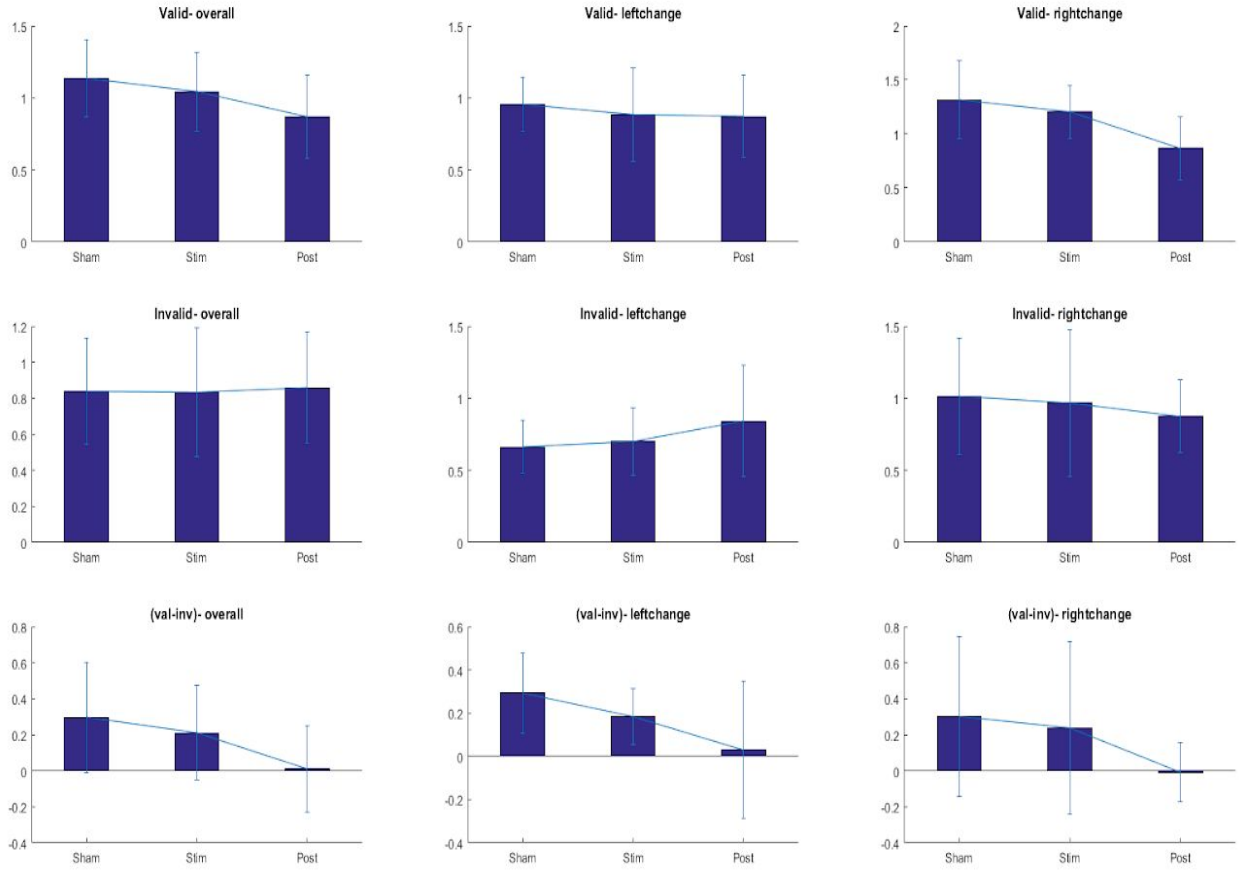


Fig. 17: Effect of right hemisphere random noise stimulation on bias. The rows indicate valid, invalid and (valid- invalid) data, whereas the columns represent overall trials, left side changed trials and right side changed trials.

These initial results suggests that a random noise stimulation does not have a consistent and significant effect on either sensitivity or bias. More number of subjects are needed to be run to have a statistically significant conclusion but these data from random noise stimulation indicate a conclusive role of tACS in modulating attention. Regardless, tACS shows promising results thus far and warrant more attention in future.

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