The Effect of Transcranial Temporal Interference Stimulation (tTIS) on Pavlovian Bias

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Preface

We approached Matthias Mittner during the spring of 2022 about being our supervisor for our thesis. It was suggested we join a study using a novel brain stimulation technique along Matthias Mittner, Gabor Csifcsák and Federica Luzzi that they were designing. We found the research both compelling and exciting. After all parties agreed this was a good fit, we joined the project in its early stages, meaning we got to take part in planning the design of the project. Although our involvement in this project ends with our thesis, the end goal is to publish a paper from our collective work. During the data collection phase, both of us had the same number of lead-experimenter and assistant roles. In writing the thesis, Andreas had main responsibility for writing the introduction, and Jostein had main responsibility for writing the method and results, with both parties contributing across sections. The discussion section was written together. Our project could not have been completed without the invaluable help from Federica Luzzi, who was an equal partner in both recruiting for and conducting the experiment. In addition, she helped by running the simulations, helped us write about the simulation parameters, and proofreading the later drafts of the thesis. We would like to thank our supervisor Matthias Mittner for his support throughout the process. His knowledge and experience with brain stimulation has been helpful to us as we navigated our way through an unfamiliar field of research. This is also true for our co-supervisor Gabor Csifcsák, whose guidance was greatly appreciated. We received valuable assistance from Thomas Nermo who aided in supplementary equipment and technical support during a time of near-continuous issues with our stimulation equipment. We are also thankful to the sanitary staff for supplying us with crucial towels. Lastly, we would like to thank all our participants for enduring our humor.

Abstract

In life, humans often approach the outcomes deemed valuable and avoid those that are harmful. This is known as the Pavlovian system. This default system is often adaptive, but it can also interfere with the more flexible instrumental system in pursuit of a goal. Research has indicated that the dorsal anterior cingulate cortex (dACC) plays a role in the arbitration process between these two systems. Due to the location of the dACC it has been difficult to focally stimulate it. Recently, transcranial temporal interference stimulation (tTIS) has been proposed as a new non-invasive brain stimulation technique to focally stimulate areas deeper in the cortex. In a preregistered, repeated measures, double-blinded study, we tested the effect of tTIS on the dACC. The participants (N = 21) completed a value-based Go/NoGo task designed to induce a conflict between the Pavlovian and instrumental system. We found no statistically significant results, leading us to speculate on whether this was due to tTIS not having its proposed effect or the dACC not responding to stimulation the way we hypothesized. These findings might have implications for better understanding the role of the dACC in decision making and for the future feasibility of tTIS.

The Effect of Transcranial Temporal Interference Stimulation (tTIS) on Pavlovian Bias

Every day we are subjected to an almost endless number of decisions to make. From choosing what to wear and eat, to choosing how we prioritize our time. We must decide whether it is best to spend our time cooking a healthy meal, or to eat a burger, and get back to working. Many of the decisions we make are founded on how we value the outcome (valence). If someone believes physical health is very important, they are more likely to spend money on a gym membership than someone who does not. This value-based decision making is an integral part of humans' everyday life. In general, humans tend to be drawn to stimuli that are typically associated with rewards, and to avoid stimuli that often result in punishments – for the most part this Pavlovian bias (PB) is a good heuristic, and it has been an evolutionary beneficial learning mechanism (Pavlov, 2010). Sometimes a conflict arises when we are met with situations that require more flexible “instrumental” learning to attain the best outcome (Raab & Hartley, 2020). To illustrate, imagine there is a berry bush, filled with appetizing berries. However, the berries are not quite ripe yet, and will still grow considerably in the foreseeable future. Here, the Pavlovian system might approach the berries straight away, as eating all the delicious berries gives a reward in the form of food and leaving them lead to punishment by not obtaining food. On the other hand, the instrumental system, as a more flexible system, is more likely to consider the long-term yield of not approaching the berries until they have matured to full size. Both the Pavlovian system and the instrumental system can make better or worse predictions concerning different situations – this would depend on several factors, like how time-consuming it would be to wait for the berries to ripen, and how much larger the yield would be after they were fully grown. Sometimes, however, the Pavlovian system can hinder the more flexible instrumental learning. In the Pavlovian system, if we learn that eating the berries immediately is positive, we might never have a reason to let the berries keep growing.

The valence that any given action has for the individual plays a large part in our decision-making. For the Pavlovian and instrumental systems this entails making a prediction about the outcome of any given action - we seek rewards and attempt to avoid punishment. Although PB is often a good heuristic, other times, when the best outcome is not so straight forward, like with the berry bush example, it makes more sense to inhibit the Pavlovian system, and instead use other means to achieve our goals. In order to better understand the arbitration of these different systems, and when we switch between them, researchers have created ways to orthogonalize the manipulation of action (approach vs. avoidance) and valance (reward vs. punishment) (Guitart-Masip et al., 2014). By creating situations that are congruent or incongruent with PB, studies have been able to not only differentiate between PB and instrumental learning, but also to look at the neural signatures of the arbitration between the two systems (Gershman et al., 2021). One of the key findings is the inverse relationship between theta band activity (4 – 8 Hz) in the midfrontal cortex and how much participants relied on PB - where higher theta power, especially in the dorsal anterior cingulate cortex (dACC), was linked to less reliance on PB. This could be interpreted to mean that theta power in the dACC reflects that more cognitive control is available – which in turn facilitates the inhibition of the PB in situations where PB is suboptimal.

The dACC is a structure located on the medial wall of the cerebral cortex, hugging the corpus callosum. Research on the dACC has been ongoing for decades, and there has been much debate on its potential functions, with some evidence pointing towards it playing a part in cognitive control (Shenhav et al., 2016). Gershman et al. (2021) also found a link between the dACC and cognitive control, saying that high inferred controllability is necessary for the exertion of cognitive control. High controllability was also linked to an increase in midfrontal theta (MFT), which they argue signals the need for cognitive control. If we think about the Pavlovian system as automatic, then it would follow that we need a high inferred controllability of the current situation to change to the instrumental system. The reasoning is that controllability is a necessary condition for predicting the outcomes of our actions. Indeed, recent research does point in this direction, showing that the Pavlovian system is more favored in low-control contexts, as opposed to contexts in which the participants have high control about the amount of reward they can achieve (Dorfman & Gershman, 2019).

Most of the research on the dACC has been done using functional magnetic resonance imaging (fMRI) to characterize hemodynamic signals on tasks specific to the scientific questions they were interested in. This research includes, but is not limited to; studies of pain, executive control, conflict monitoring, and salience processing (Lieberman & Eisenberger, 2015). The debate regarding the function of the dACC is anything but settled, and its true role would likely need a new integrative model, that can properly explain its part in diverse areas. Attempts to make integrative models have been done decades ago (Bush et al., 2000) as well as more recently (Heilbronner & Hayden, 2016), but the lack of consensus (Wager et al., 2016), may indicate that we still need more research on the dACC before we truly understand its functions. Studies on the dACC have historically been on lesions on the dACC, as well as neuroimaging during tasks. More recently researchers have also started stimulating the dACC through the means of non-invasive brain stimulation (Piretti et al., 2022; Onoda et al., 2017).

None-invasive brain stimulation (NIBS) is a method of modulating neural processes in the brain, which enables researchers to study how altered neural activity affects behavior. The two most established techniques are transcranial magnetic stimulation (TMS), that uses electromagnetism, and transcranial electrical stimulation that uses weak electrical currents (Polanía et al., 2018). Two common forms of transcranial electrical stimulation are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). One meta-analysis pooled 19 studies on NIBS, and found inconsistent, but overall positive effects on alleviating symptoms of Alzheimer's disease (Teselink et al., 2021).

Another meta-analysis on the NIBS techniques tACS and TMS looked through 82 studies effects on cognitive functioning in brain disorders. They found only a small effect but conclude that this might be enough to improve daily function (Begemann et al., 2020). To date, employing non-invasive techniques to stimulate deeper brain areas (deep brain stimulation, DBS) has proven much harder, as NIBS techniques have a limited reach and will also stimulate the surrounding layers of the brain. On the other hand, invasive techniques are capable of sub-cortical DBS, by surgically inserting electrodes into the brain. Such techniques have shown remarkable effects on for example treating advanced Parkinson's disease by stimulating the subthalamic nucleus (Benabid et al., 2009), but have the trade-off of being both more dangerous, expensive, and time-consuming (Fenoy & Simpson, 2014), and are therefore only suitable for a very limited subset of patients. As such, it would be beneficial to achieve deep brain stimulation with a more practical and safe NIBS approach.

Recently, a novel method, transcranial temporal interference stimulation (tTIS), has been proposed as an alternative NIBS method. In theory it should be able to achieve both focal and steerable brain stimulation, while also being capable of DBS with reduced stimulation of the surrounding areas (Grossman et al., 2017). TTIS is achieved by applying two high-frequency tACS stimulators to the scalp with two electrodes connected to each stimulator. The two oscillating electric fields interact and result in a low-frequency amplitude-modulated field, the envelope of which oscillates at the difference frequency of the two applied fields. The concept of tTIS is based on universal neurons' properties, in particular the intrinsic low-pass filtering of electrical signals by the neural membrane (Hutcheon & Yarom, 2000) which prevents neural electrical activity from following electric fields oscillating at high frequencies (e.g., 1000 Hz). For this reason, stimulation with high frequencies is assumed not to affect the neurons' resting membrane-potential. If two stimulators' frequencies have a difference equal to a frequency within the physiological range (e.g. $f1$= 1000 Hz, $f2$=

995 Hz, *$\Delta f=5$* Hz), it could be possible to modulate neurons with the difference frequency (i.e., 5Hz) exclusively. This mechanism facilitates the stimulation of deeper brain structures where the two fields meet and is one of the main proposed benefits of tTIS over tACS.

For exploring the realm of possible uses, advantages, and applicability of this new method, a number of computational studies were done. A study by Rampersad et al. (2019) corroborated findings and explored several of the assumptions made by Grossman (2017). Using their computational models, Rampersad et al. (2019) concluded that tTIS was capable of suprathreshold modulation, i.e., stimulating action potentials in neurons, in rats. This was not the case for human head models, as the safety guidelines limiting the intensity of the electrical current applied result in insufficiently strong electric fields to penetrate the human skull and reach deeper brain regions with enough strength needed for suprathreshold modulation. However, tTIS simulations could achieve subthreshold modulation, i.e., induce a current capable of modulating neurons by reducing the resting membrane-potential, for those same deep brain regions. This level of stimulation was comparable to the strength achievable by traditional tDCS, but importantly, the tTIS simulation achieved these levels with higher focality, resulting in less unwanted stimulation in the regions above the target. Rampersad et al. (2019) conclude that tTIS is not capable of replacing DBS but can be used for subthreshold modulation and potentially has several advantages for stimulating deeper brain regions compared to tDCS.

The theoretical background for tTIS and the way it modulates brain activity might not be as simple as previously suggested (Mirzakhalili et al., 2018). Grossman et al. (2017) theorizes that tTIS works due to the low-pass filtering of neurons, but Mirzakhalili et al. (2018) argue this is unlikely to be the case. This is due to the nature of the envelope created by tTIS, which contains high frequency elements oscillating at the target frequency, that are not modulated by the low-pass filtering alone. The oscillations require rectification in order to modulate the neurons, in other words, a mechanism that converts the oscillating high frequency elements into sinusoidal waves that can entrain the neurons. They argue that this can be achieved in the brain, but via the ion-channels in the axon. This theoretical distinction has several practical implications according to Mirzakhalili et al. (2018), the most important of which is the potential for stimulation blocking. A phenomenon that occurs at high frequency stimulation, where the surrounding area of the region of interest (ROI) experiences a reduction in neural excitability. This stimulation blocking effect is more concerning as the field strength increases, and for the strength used in this study it is less likely to have this effect. They argue that further studies using computational modelling should consider which areas are inhibited, not just which areas are stimulated.

So far, studies on tTIS have mostly been limited to computational studies (Rampersad et al., 2019; Conta et al., 2021), as well as experiments on animals (Song et al., 2021) and human cadavers (Acerbo et al., 2022). The first two studies of tTIS on healthy human subjects were published in 2021, followed by another two in 2022 (Conta et al., 2022; Zhu et al., 2022; Wessel et al., 2021; Ma et al., 2021). Three of them successfully modulated the excitability of areas in the motor cortex (Zhu et al., 2022; Wessel et al., 2021; Ma et al., 2021), while Conta et al. targeted a ROI located superficially in the occipital lobe. Conta et al. used three conditions; tTIS, tACS and a sham tTIS that used the same frequency on both stimulators, e.g., 1000/1000 Hz, which in theory should have no modulating effect. Interestingly, they found no significant difference between the three conditions, leading them to conclude that either the established technique of tACS (Kasten & Herrmann, 2017) did not have any modulating effect, or that the sham condition they used did have an effect. Therefore, they suggested that any new studies on tTIS should test both tTIS, the fake tTIS Conta used as a sham condition, as well as a sham condition without any stimulation.

The underlying neural mechanism that gives rise to midfrontal theta oscillations is not fully known, and is unlikely to have a uniform function, as it is broadly distributed across the brain and connected to high-level cognitive processes, such as memory encoding, working memory, and facilitating top-down cognitive control (Cavanagh & Frank, 2014). Cavanagh and Frank (2014) tried to compare the descriptive research done on the frontal theta band in the medial prefrontal cortex (mPFC) and put forth some possible explanations for how these functions are propagated, using evidence from EEG. They found evidence for MFT being a "surprise" signal, both in connection to uncertainty that is unexpected and expected, where in both cases the surprise or feedback indicates a need for cognitive control. This surprise signal has been linked to subsequent switching of tactic, for instance the increase in accuracy at the cost of response time, indicating a more careful approach to the relevant task. This effect might be possible due to the cross-cortical connectivity of the mPFC and its ability to facilitate synchronicity in the common theta band frequency when cognitive control is needed (Cavanaugh & Frank, 2014).

Given the current research of the role MFT has on the dACC in the matter of the arbitration between PB and instrumental learning, we wanted to test whether stimulating the dACC in the theta band frequency, would have a faciliatory effect on the ability to inhibit PB in an orthogonalized Go/NoGo task. In order to successfully stimulate the dACC, we would need a technique capable of DBS, without also stimulating outside our ROI. We therefore decided to use tTIS to stimulate the dACC on 21 healthy human adults, while playing a computer-based card game that orthogonalizes action and valence with a Go/NoGo task. Given this, we formulate our hypothesis as follows: we expect that modulating the dACC in the theta band frequency will decrease PB on our Go/NoGo task, compared to no stimulation and sham conditions.

Methods

Participants

Due to practical limitations of this pilot study, we recruited 22 participants. One participant had to be excluded due to issues with stimulation. We collected data from a sample size of 21 healthy adults (age range 22-32, M = 26.75, SD: 2.73, 11 females). We ran a sensitivity analysis with G-Power (Faul et al., 2007), and with this sample size we are able to discover a minimal effect-size of d = 0.56 with alpha = 0.05 and power = 0.8. Ethics approval was obtained from the institute for psychology's ethics committee (IPS-REC, https://en.uit.no/research/ethics/ips) before recruitment began. Participants were recruited by posters on the university campus, online, and personal contact, and were included and excluded in accordance with the criteria listed in the informed consent (https://osf.io/46y9z). Briefly summarized these criteria are that the participant had to be healthy (without neurological disorders), between 18 and 50 years old, without metal implants or using central stimulants at the time of the experiment (caffeine was allowed within their normal use). Participants were told that they would receive 300 NOK with the chance to win an additional 100 NOK if they performed well in the task. This was to ensure that participants were motivated to perform well on our Go/NoGo task. However, unbeknownst to the participants, all participants received the full 400 NOK independent of their actual performance. The sessions were scheduled with a minimum gap of 48 hours to mitigate potential long-lasting effects of the stimulation protocols. The maximum gap between two sessions was set to two weeks. Data was collected between 07.10.22 and 18.11.22. Participants were required to produce at least one Go and one NoGo response in each block of our reinforcement learning (Go/NoGo) task for the data to be included in our analysis. None of the participants failed to meet this requirement.

Design

We used a fully within-participant, counter-balanced, double blinded repeated measure design. Participants underwent the three sessions in a randomized and counterbalanced order. Each session contained three blocks of the task. The first block was done without stimulation and served as a baseline. During the second and third block, one of three stimulation conditions was administered. We used double blinding, meaning neither the participant nor main experimenter knew which stimulation was applied in each session. Blinding was achieved by having an assistant that kept track of the stimulation condition and was responsible for activating the two stimulators. The display window on the stimulators were also covered for the duration of the experiment session. The three possible stimulation conditions were Real tTIS, Active-sham, and Sham. The Real tTIS was the active condition with 3 mA current intensity, 250 Hz in one stimulator and 245 Hz in the other stimulator, generating the needed envelope for tTIS stimulation. The Active-sham condition had 3 mA current intensity, 250 Hz in one channel and 250 Hz in the other channel. In this condition the high frequencies should not create an envelope in a range conducive of brain stimulation and was not expected to produce a physiological effect. Our Sham condition included a fade-in period of 4 seconds, after which, a 3 mA current intensity with 250 Hz in one channel and 250 Hz in the other channel is administered for 30 seconds, followed by a fade-out period of 4 seconds. After the fade-out no electricity was administered for the rest of the session.

The outcome variables we measured were based on task performance quantified in terms of both accuracy and a Pavlovian Performance bias Index (PPI). The PPI is based on the mean of the two indices “Reward-based invigoration” (RBI) and "Punishment-based suppression (PBS)". RBI was calculated as the number of "Go" responses to "Win" cards divided by the number of all "Go" responses, while (PBS) was calculated as the number of "NoGo" responses to "Avoid" cards divided by the number of all "NoGo" responses.

Response times were also measured but was not used in our analysis. The independent variables are the block for the card game (baseline, stimulation block 1 and stimulation block 2) and type of stimulation administered during each session. In addition, we collected participants' self-ratings of controllability and success after each block, the guesses of the experimenter and participant for which stimulation condition was administered, and any self-reported adverse effects following the stimulation.

Simulation parameters

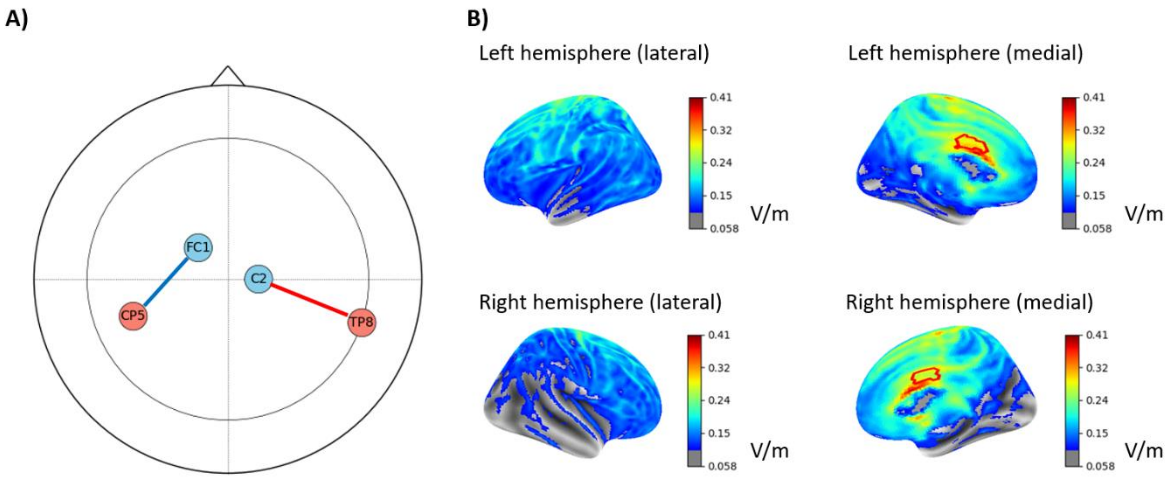
Simulations of the electrical fields were used to establish the tTIS electrode montages needed to effectively target and stimulate the dACC. To this end, MATLAB R2018b and the SimNIBS 3.0 toolbox (Thielscher et al., 2015) were used to combine the two electrical fields into a temporal interference field. The spatial distribution of the envelope modulation amplitude was computed with the formula used by Grossman et al. (2017) implemented in a MATLAB script (Thielscher, 2020).

For the electric field simulation, simulated rubber electrodes with a 3x3 cm dimension were used. The SimNIBS 3.0 software allows to model the electrodes and conductive gel's thickness that were set to be 0.5 and 1 mm, respectively, mimicking the setup of our study. The tTIS simulations were run with 3 mA (peak to peak) per electrode pair, which was the maximum intensity supported by our stimulators. We simulated the electrical fields generated by a multitude of different electrodes montages. We used the 10-20 electrode system as reference for the placements of the electrodes (Jasper, 1958). Many computational studies use the Montreal Neurological Institute (MNI) brain, a standard brain generated from 152 MRI scans on normal controls, therefore we decided to run the simulations on this head model. The ROI, the bilateral dACC, was established based on the Schaefer atlas with 300 parcels and 17 resting-state networks (Schaefer et al., 2018).

Our goal for the simulations was to find the optimal montage able to target the left and the right dACC with highest possible intensity in the ROI and least possible intensity in other regions. More than 600 simulations were run with different montages. The choice of the different montages was based on educated guesses for the electrode positions and were iteratively refined based on our increasing experience. In order to select the best montage, average and maximal electric field strength indices within the (bilateral) dACC as well as a focality index (i.e. the proportion of surface elements in the dACC that were within the upper 1% percentile of all E-field values across the whole cortex) were calculated. In addition, we generated visualizations of the electric fields induced by the different montages for a more qualitative assessment (see Figure 1b for an example) for each simulation. Preliminary selections were done visually, then the resulting promising simulations were sorted based on several indices for focality and delivered current in the ROI. Finally, we used visual inspection of the distributions to converge on our final montage. The C2-TP8 and FC1-CP5 electrode montage was considered optimal and was selected for the current study.

Figure 1.

The Montage Used for Stimulation



Note. **A)** The electrode position used for stimulation. **B)** The resulting electrical field strengths achieved with our montage shown on surface models. The red outline is dACC based on the Schaefer atlas (Schaefer et al., 2018).

Equipment

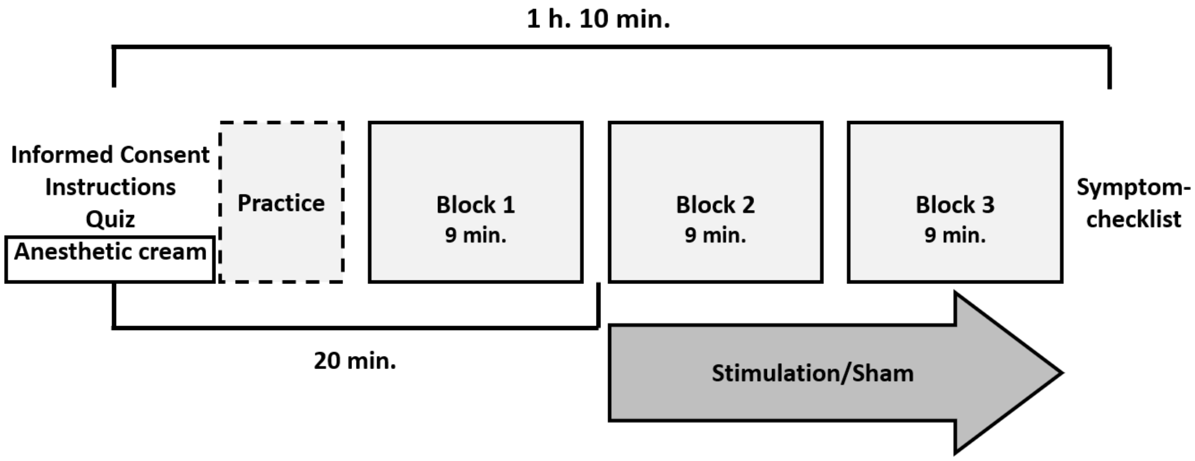
We used two NeuroConn DC stimulator plus devices (NeuroConn Gmbh, Ilmenau, Germany) for this study. To deliver the current, we placed four Neuroconn 3 cm x 3 cm rubber electrodes with conductive paste Ten20 (Weaver & Co, Aurora, CO, USA) placed using the international 10-20 system, at the locations C2-TP8 and FC1-CP5. The maximum frequency possible with our NeuroConn DC stimulator plus device was 250Hz and therefore, this frequency was used as the carrier frequency. Before applying the conductive paste, the skin in the predefined surface regions was cleaned with alcohol swabs, after which a small amount of a local anesthetic cream (Emla, 25mg/g, Aspen Pharma Trading Limited, Dublin, Ireland) was applied to the scalp surface at each of the electrode positions to make the different conditions harder to distinguish for the participants. Impedance values, which is a measure of the connection established with the scalp, were kept below 15 kΩ for the stimulations.

Procedure

The experimental sessions were all conducted by a main experimenter that communicated with the participant, and an assistant, that aided in the placement of electrodes and started the stimulation. The condition for stimulation was dictated by a randomization list that was not accessible to the main experimenter (i.e., the assistant ensured blinding of the experimenter). After reading and signing the informed consent, both experimenters measured the participants' head for fitting the EEG-cap. Then, using the EEG-cap with the 10-20 system the locations for each electrode were marked with a non-permanent pen. The marked area was washed with alcohol and the anesthetic cream was administered on the area roughly corresponding to the size of the electrode. While the cream was given time to numb the area (20 minutes) the participant read the instructions for the computer-based card game. They were informed that the goal of the game was to collect as many points as possible by either picking up, or not picking up the cards shown. The cards were either “winning” or “losing” cards, and that Win cards would either provide a reward (10 points) or zero outcome, whereas Avoid cards could result in a loss (-10 points) or no reward (zero points). Participants were informed that the correct response (picking up the card, or not picking up) for each card would most likely give the correct feedback, but that there was a certain probability for the wrong feedback to be given for a correct response. During the first session all the participants completed a practice session of the card game; for the second and third session they were given a choice to either complete it or not. After the training session, participants answered a quiz about the rules of the card game, where any mistakes were highlighted and corrected by pointing to the relevant section of the instructions. Once sufficient time for the anesthetic cream to become effective had passed, the electrodes were placed using the Ten 20 conductive paste on the marked areas. Once satisfactory impedance levels were reached, the first block of the task was started without turning on the stimulation. After the first block was completed, the stimulators were started by the assistant responsible for blinding. While the stimulation was active (approximately 20 minutes), participants performed two more sessions of the card game. At the end of each block, they were asked to answer to which degree (on a visual analogue scale) they felt successful in their performance and whether they felt they were in control of the outcome. Between the blocks there was an optional minute break. After the last block, participants would fill out a symptom checklist for documenting any adverse effects of the stimulation. The procedure is summarized in figure 2.

Figure 2.

Procedure



Note. An example of an experimental session procedure, informed consent is collected only during the first session.

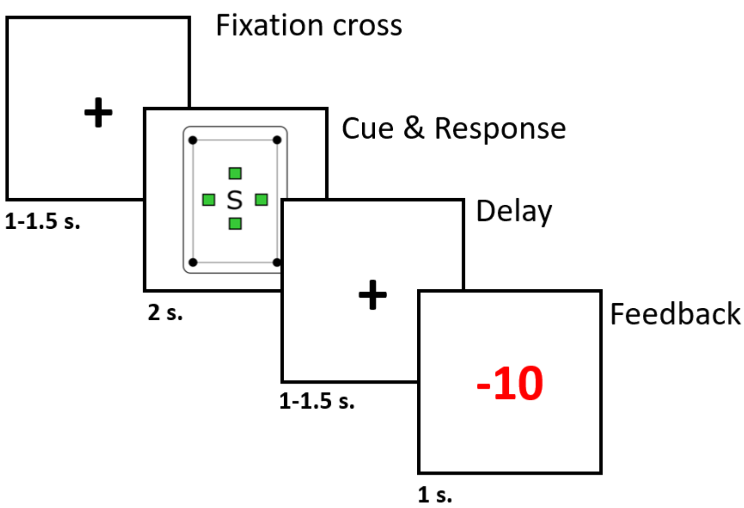
Task

The card game is a Go/NoGo task that orthogonalizes valence and action, using four possible combinations, where two conditions are congruent with Pavlovian response-tendencies (go-to-win and nogo-to-avoid) and two conditions being incongruent with the Pavlovian system (nogo-to-win and go-to-avoid). The participants' responses are reinforced probabilistically, where a correct response would result in a 70 percent chance of receiving a reward/avoid punishment in case the response was correct and 30% chance in case of an incorrect response. The second and third block were identical to the first except with different cards, consisting of 80 trials per block (four cards with 20 repetitions). Trials started with a central fixation sign, followed by a stylized card, a short delay, and the outcome (see Figure 3). To "pick up" the card the participant had to press spacebar during the time the card was shown. The task consists of three blocks with the same rules. Each block implemented a new set of cards that was never previously seen by the participant. All cards contained a letter or symbol and colored geometrical shapes to make recognition easier (https://osf.io/xr4mu?view_only=133a51b5a1004ad7b63a85aa22ed6ff6). Each session had different scripts for the order of these scripts were randomized for each participant.

For running the task, we used a LENOVO laptop with Windows 10 operating system, Intel (R) Core (TM)i5-6200U CPU, 2.30 GHz, 8 GB RAM, and a 13” monitor with 1920 x 1080 resolution and 48 Hz refresh rate. Stimuli were presented and responses were collected using PsychoPy 1.83.04 (Peirce, 2007).

Figure 3.

Illustration of a Single Trial of our Go/No-go Task



Statistical Analysis

Our analysis strategy for both Accuracy and PPI was to start with repeated measure analyses of variance (rmANOVA) to test for overall effects of stimulation, block, and their interaction. In the case that stimulation condition would influence performance in the task as indexed by accuracy and PPI, we would expect an interaction between block and condition (since the stimulation became active in block 2). In order to quantify evidence in favor of the null-hypothesis and make potentially non-significant results more interpretable, we performed an equivalent Bayesian analysis. We used Jasp (Jasp Team, 2022) to conduct these analyses and used the default priors implemented in Jasp (r scale for fixed effects=0.5, r scale for random effects=1.0 and a uniform prior for the model). Specifically, we report the Bayes Factor in support of the null-hypothesis, BF_{01}. The value of this Bayes Factor quantifies how much more likely the null-hypothesis is when compared to the alternative hypothesis given the data (i.e., a $BF_{01}=9$ indicates that the null-hypothesis is 9 times as likely as the alternative).

Following up on that global analysis, we then tested our main hypothesis by means of a series of paired, one-tailed t-tests with a significant level of 0.5. These specific contrasts were pre-registered at the Open Science Framework (https://osf.io/qkrvu). Stimulation was turned on in the second and third block, therefore, we would expect an effect with the number of block (B1, B2 and B3) and the type of stimulation tTIS (Real tTIS, Active-sham and Sham) on the dependent variables Accuracy and PPI. Regarding our first set of hypotheses, we expect that the accuracy for incongruent cards will increase with stimulation. Comparing the difference in accuracy from block 2 with 1, and the difference in accuracy from block 3 with 1, should result in a larger difference for the Real tTIS, than for Active-sham and Sham. For PPI, we expect that the B2-B1 and B3-B1 difference will be a lower value in the Real tTIS condition compared to the Active-sham and Sham. Since better performance will manifest itself by decreasing measure of PPI (closer to 0.5) compared to a performance more affected by PB (PPI closer to 1).

The Response time (RT) was recorded, but not analyzed in our study. This was due to a segment of participants not, or very rarely, picking up the go-to-avoid cards. This caused missing data for five participants, and for participants that rarely picked up go-to-avoid cards, the RT was based on very few trials, increasing variance and outliers. This behavior is in line with PB and caused high levels of PPI for some of the participants. This relationship was descriptively investigated.

Results

Main analyses

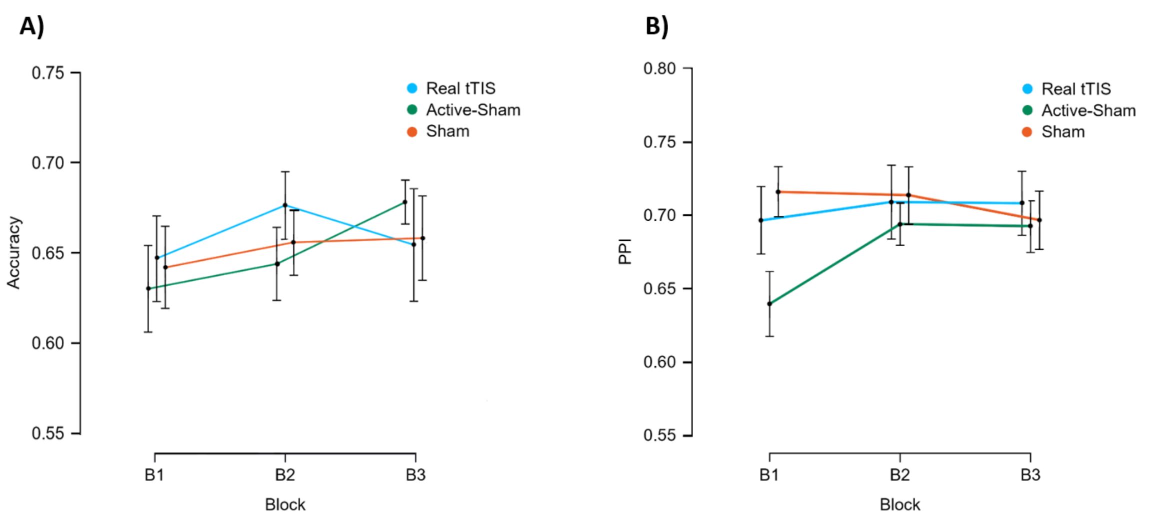
We tested the overall effect of stimulation and block on Accuracy with a repeated measures ANOVA and found no main effect for both stimulation $F(2,20) = 0.07$, $p = .93$, $\eta_p^2 = 0.003$, $BF_{01} = 7.3$, and block $F(2,20) = 1.17$, $p = .32$, $\eta_p^2 = 0.055$, $BF_{01} = 5.5$. There was no significant interaction effect $F(4,20) = 0.68$, $p = .61$, $\eta_p^2 = 0.030$, $BF_{01} = 396$, with strong evidence against an effect (van Doorn et al., 2021). For PPI neither the effect of stimulation $F(2, 20) = 1.47$, $p = .24$, $\eta_p^2 = 0.068$. $BF_{01} = 3.0$ or block $F(2,20) = 1.15$, $p = .33$, $\eta_p^2 = 0.054$, $BF_{01} = 6.5$, were significant. The interaction effect $F(4,20) = 1.15$, $p = .34$, $\eta_p^2 = 0.054$, $BF_{01} = 91$ did not reach significance and the BF indicated strong evidence for H_0. In summary, the global analyses did not support an effect of stimulation on performance and the Bayesian analysis suggests strong evidence for the absence of such an effect. For a descriptive plot of both analyses, see Figure 4.

To test our hypotheses more directly, we followed the analysis plan specified in our pre-registration document (https://osf.io/qkrvu) which involved direct comparisons of the expected stimulation effects for the dependent variables Accuracy and PPI. We performed one tailed paired t-tests for Accuracy and PPI with the hypothesis that the difference between blocks would be increased for the Real tTIS condition. There was no significant difference in Accuracy between Real tTIS and Active-sham for B1-B2 $t(20) = -0.5$, $p = .69$, or B1-B3 $t(20) = 1.3$, $p = .10$. The same was true for the difference in Accuracy between Real tTIS and Sham for B1-B2 $t(20) = -0.0$, $p = .52$, or B1-B3 $t(20) = 0.7$, $p = .25$. Similarly, there was no significant difference for PPI between Real tTIS and Active-sham for B1-B2 $t(20) = -1.1$, $p = .86$, or B1-B3 $t(20) = -1.2$, $p = .87$. This was also true for the difference in PPI between Real tTIS and Sham for B1-B2 $t(20) = 0.5$, $p = .30$, or B1-B3 $t(20) = 0.8$, $p = .21$. Taken together this indicates that neither the performance on the task nor our measure of Pavlovian bias was affected by the stimulation in any of the blocks.

Interestingly, we had two main groupings of data for PPI. These two groups were participants with high PPI (meaning a higher tendency to rely on Pavlovian bias) and participants with low PPI (those that relied less on Pavlovian bias). With the former more often indiscriminately picking up cards with the possibility of giving a positive reward, and/or rarely picking up those that could cost them. Dividing by the mean value of PPI, we ended up with the grouping of 13 with low PPI (*M* = 0.56, *SD* = 0.05) and 8 with high PPI (*M* = 0.91, *SD* = 0.05), with no participants having an average PPI value between 0.65 and 0.83.

Figure 4.

Descriptive Plot for Accuracy and PPI



Note. **A)** An interaction plot of the means for all conditions for Accuracy, error bars represent standard errors. **B)** An interaction plot of the means for all conditions for PPI, error bars represent standard errors.

Additional analyses

We checked the efficacy of our double-blinding procedure by using a chi-square test for both experimenters (i.e., the main experimenter and the assistant). For the experimenters the relationship between condition and condition guessed was not significant $X^2(4, N = 63) =$

4.8, p = .3, indicating that the experimenters could not guess correctly above chance level. The participants were only told to guess between sham and real stimulation since they were unaware of the Active-sham condition. Because of that structure, a corresponding chi-square analysis cannot be conducted. However, looking directly at the data for the guesses, most participants guessed real tTIS independently of the stimulation they were subjected to, with 90% guessing real during Real tTIS, 74% guessed real during Active-sham and 47% guessed real during Sham. Two out of 21 participants guessed correctly for all three sessions, and eight guessed they received real stimulation every time. We evaluate this to be evidence for our blinding being successful, and participants not being able to tell the difference between real stimulation and our sham conditions.

The symptoms reported in the tTIS-checklist were rated on how likely it was due to the stimulation as either: no (1), unlikely (2), possibly (3), likely (4), definitely (5). Out of the 132 symptoms that were reported to be due to the stimulation the three most common adverse effects were tingling (36), itchiness (18), and fatigue (18). The symptoms could be rated as either: none (1), mild (2), moderate (3), or severe (4). Most symptoms reported were mild (69%). Severe symptoms were reported five times (itchiness, tingling, pain on head, issues with concentration, and sudden mood change). In all cases the symptoms seized after stimulation and were not evaluated to be a serious issue.

Discussion

We set out to test our hypothesis that stated that stimulating the dACC using transcranial temporal interference stimulation at theta frequency would result in a reduction of Pavlovian bias in a decision-making task. The results did not support this conclusion, as we did not observe any reduction in Pavlovian bias or accuracy. Having used both an active-sham and a true sham condition, we can be reasonably confident that our failure to find an effect of the active stimulation protocol is not due to an unintentionally effective active-sham condition

(Conta et al., 2022). Hence, we are left with two main hypotheses about why the stimulation had no significant effects: Either the actual properties of tTIS do not have the effect that our simulations indicated or stimulating the dACC does not actually have the effect that we theorized. Conversely, the lack of any significant effects could be caused by limitations with our design. In the discussion we will go into detail on these limitations, as well as some theoretical challenges with both the dACC and tTIS.

Decision-making has been thoroughly investigated through a plethora of studies the last half-century, mostly using tasks (Weiss & Shanteau, 2021). More recently the use of NIBS has also been used to study decision-making (Levasseur-Moreau & Fecteau, 2012), yet the dACC has still not been focally targeted with NIBS regarding Pavlovian bias. Although studies do indicate that decision-making can be modulated with tDCS and TMS (Levasseur-Moreau & Fecteau, 2012), this has not been tested using tTIS. This may be because the location of the dACC renders it difficult to reach without also stimulating the surrounding areas. For instance, in a study conducted by Csifcsák et al (2021), they tested the effects on PB with HD-tDCS on the mPFC and they hypothesized that, based on their simulations, their montage might have also reached the dACC. If they did in fact stimulate the dACC, they would also have stimulated a broader part of the mPFC, making it difficult to discriminate as to where the effects originated. As such, even if HD-tDCS could reach the dACC, it would not be focal enough for what we set out to test, as we are specifically interested in how the dACC relates to the arbitration of PB and instrumental learning.

When studying the neural signatures of arbitration between Pavlovian and instrumental action selection, Gershman and his colleagues (2021) found, using a comparable Go/NoGo task to what we used, that higher MFT was correlated with lower PB. We hypothesized that stimulating the dACC in the theta band range would make it easier for our participants to inhibit PB, by increasing MFT through entrainment. We found no supportive evidence of this hypothesis. If we assume that we were successful in stimulating the dACC with our tTIS protocol, then we would also have to accept that either MFT has a different role in the arbitration process than what we hypothesized, or that entrainment of the theta frequency does not work like expected. Although data supports the idea that theta in the midfrontal cortex is correlated with inhibiting PB (Gershman et al., 2021), we do not know if the presence of theta waves is what makes inhibiting PB easier, or whether the increase in theta band power happens because we are inhibiting PB or something else entirely. If the stimulation worked, then either our data is not congruent with the idea that having more access to theta waves is what makes inhibiting PB easier, or that the entrainment process is different to what we expected.

In a study conducted by Cavanagh and his colleagues (2013) using an orthogonalized Go/NoGo task, they reported a peculiar way that their participants scores grouped together on PPI. They named one group “learners” (less PPI, meaning less reliance on PB) and the other “non-learners” (higher PPI, indicating a larger reliance on PB). Interestingly, we found that our participants showed a similar tendency to cluster either around low or high average PPI, with the middle being void of participants. We do not know how this tendency to group together would influence our data, and there is a lack of research on what constitutes a learner vs. non-learner. One could speculate that non-learners have not fully grasped the principles of the Go/NoGo task, and therefore would have no benefit from stimulation, as they might only inhibit the Pavlovian system in response to conflict if they perceive it as a conflict.

The results from previous temporal interference studies with human brains are mixed, with three studies focusing on the motor cortex and seemingly finding reliable results, while one focused on parieto-occipital areas which did not find any evidence of an effect (Conta et al., 2022). Other non-invasive transcranial electric stimulation methods such as tDCS have previously been criticized for a lack of consistent effectiveness. In a meta study on the neurophysiological effects of transcranial direct current stimulation, Horvath et al. (2015a) found that measures of motor cortex excitability were a more reliable effect than most, if not all other achieved by tDCS. There are limitations with the study as remarked by Horvath et al. (2015a), and the result cannot be extrapolated to the whole field of tDCS research, as behavioral modulation was not included in the analysis. In a response to the article Antal et al. (2015) mention several other issues and mistakes that further complicates drawing conclusions from it. However, if we assume motor cortex excitability was the only replicable physiological result achieved with tDCS, such a finding would be in line with the distribution of the results for the existing studies on temporal interference.

In another review, Horvath (2015b) failed to find any cognitive effect of tDCS on healthy adults in several broad cognitive domains, when looking at post-stimulation outcome scores for single session tDCS. Again, there was some theoretical discussion surrounding these results, with Chhatbar (2015) later arguing effects could be found when accounting for group variability. Regardless of the outcome of these theoretical contentions, both of Horvath studies (2015a, 2015b) and a growing number of failed replications and conflicting results (Csifcsák, 2019) point to an uncertainty about the effectiveness of tDCS in the field. This difficulty of achieving consensus could be due to several factors, like the lack of sham conditions, blinding and all data not being reported. The lack of shared data for example, makes it harder to pool results and compare effects across studies. More generally, it has been argued that both tDCS and tACS has problems with the absence of replication studies, along with the missing methodological consistency (Bestmann & Walsh 2017) across studies. This of course, is a problem in line with the recent concern of low replicability in psychology research as a whole (Open Science Collaboration, 2015). Making sure these limitations are dealt with will be important for a line of research as new as tTIS. Future studies striving for methodological consistency and a transparency in reporting results could contribute to the integrity of the research field going forward and make reliability of tTIS easier to assess.

There are multiple other reasons for why tTIS might not have had an effect on behavior in our study. It could be due to uncertainty with the placement of the electrodes, the strength of stimulation, limitations of our equipment, or practical issues with the principles of tTIS. Placement of electrodes is inherently an uncertain procedure, from the underlying theory used in deciding the placement, to placing them in practice (De Witte et al. 2018). This is especially pertinent for the field of tTIS with the possible increase in focality, where even small deviations could substantially affect the stimulated area, as is the case with our relatively small ROI (figure 1b). We could have used individualized placements to account for the variability in the electrical field across subjects (Conta et al., 2020). In our study we did not have the individual neuroimaging to assist in locating the dACC, as we used the average model brain of (MNI) in our simulations. Deciding on highly specified locations on an average brain is not necessarily conducive to an increase in error but it is a balance of specificity and generalizability one must consider. For placing the electrodes in practice, we used the 10-20 system which is less reliable than placements using neuronavigation based on individual MRI scans (De Witte et al., 2018), and the natural contribution of human error which was not compensated for by having MRI to confirm which area we ended up stimulating. Moreover, we were not able to individualize the theta frequency for each participant. Our chosen frequency, 5Hz, approximates the theta range (4 – 8 Hz), but there is evidence for an individualized frequency outperforming static frequencies like our approximation (Zhang et al., 2022).

Our simulations indicated our electrode placement would produce a field strength of around .3 and .4 V/m in the defined ROI. This is higher than what has been found to produce effects for tACS (Johnson et al., 2020), which had lower field strengths and found the potential effect increases with higher field strength. The equipment we used could only produce a sinusoidal electrical field in a frequency of up to 250Hz, this is not in line with the recommended limit postulated by Grossman and could be able to interfere with natural brainwaves. This could create an effect for the Active-sham and increase excitability, hindering clear results in our study. This limitation was mitigated by including a sham condition without stimulation. Meaning we could directly compare with the non-stimulation condition, where neither the results for Real tTIS or Active-sham were different from the Sham, indicating the frequency of 250Hz did not influence our data. The effect of frequencies in this range has been found to be modulated by the change in frequency in a broader range (Moret et al., 2019), and we know of no research that would indicate our stable 250 or 245Hz stimulation would produce effects in the surrounding areas.

The empirical support for the methodological soundness of temporal interference is still in its early stages and more research on the principles is required. When possible, studies using tTIS should employ neuroimaging techniques in both the placement of the electrodes and in the measure of the effect achieved. Further studies on temporal interference should use more agreed upon areas for stimulation, thus reducing the possible degrees of uncertainty. This point is also important for the task used, where previous evidence of increased activity is needed. This is because tTIS modulates excitability, and better understood relationships between task demands and brain activity is necessary for drawing conclusions about the role of stimulation. This will also make replication easier and contribute to a more robust field of research.

Future research on the dACC regarding decision-making should focus on combining neuroimaging techniques with tasks that induce the arbitration of PB and instrumental learning. We would suggest that looking more closely at learners vs. non-learners on our Go/NoGo task could give valuable insight into how and when MFT is used. For example, a future study could investigate if non-learners had more MFT available after receiving more training on the Go/NoGo task. In a study where Guitart-Masip and his colleagues (2011) found that non-learners did comparable to learners after training more on the task, they did not investigate if this also raised their MFT-levels. We believe that a better understanding of the group differences we seem to find between learners and non-learners is needed, as this could have implications for those that potentially could take advantage of theta band stimulation in the dACC in order to inhibit PB, as well as expand our understanding of decision-making regarding the Pavlovian and instrumental systems. Previous studies on interactions between the Pavlovian and instrumental system have implemented computational models of learning. These models have been shown to have a more sensitive and sophisticated representation of the learning process that takes place during decision-making tasks. These models account for more parameters than conventional analyses, including the interplay of feedback and balancing different biases, like implemented by Csifcsák et al. (2020). This allows for isolating the behavioral parameter of interest, making it possible to analyze it more directly. The data collected in our study will be used to make future computational models, and we believe this can give valuable insights into our participants' decision-making process.

We used a fully within-participant, counter-balanced, double blinded repeated measure design for our novel non-invasive brain stimulation study. Stimulating the dACC using tTIS had no significant effects on our orthogonalized Go/NoGo task, leading us to speculate on whether this was due to tTIS not working or the dACC not responding to stimulation the way we hypothesized. Given our results, we have suggested several practical and theoretical considerations for future research. Our study lends itself to the growing body of literature that may help discover both the functions of the dACC and the future feasibility of tTIS.

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Appendix

Following with the principles of open science, all materials and data for this study are available at https://osf.io/rc756/?view_only=133a51b5a1004ad7b63a85aa22ed6ff6