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Quantifying Placebo Using tDCS and Subject Expectancy

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Specific Aims

In a clinical setting, doctors often rely on patients to self-report how they feel after a treatment. Currently, we do not quite know whether or not a placebo treatment interacts with a person's metacognitive sensitivity, and this is information that is vital to the treatment of practically any ailment, physical or otherwise.

The placebo effect can be described as a set of positive or negative changes that occur in response to a placebo treatment—one that has no actual therapeutic value—often paired with the context in which this treatment is administered [1]. Expectations, of the subject and researcher alike, exert a strong influence on the strength of the placebo effect and have been shown to exacerbate subject responses to inert treatments [1–4]. Metacognitive sensitivity, the efficacy with which confidence ratings discriminate between correct and incorrect answers [5,6], could be affected by the placebo effect.

Thus, we propose to study the effects of inducing the placebo effect via verbal expectancy cues to participants while they undergo bilateral transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) and perform a visual perception task. DLPFC is known to be important for working memory [7], decision making [8,9], metacognition [10], and has been indicated as being involved in the placebo effect [11]. Simultaneously, we are also studying the effects of bilateral high definition transcranial direct current stimulation (HD-tDCS) of the dorsolateral prefrontal cortex (DLPFC) on task performance and metacognitive sensitivity as there is an ongoing debate regarding the effects—or lack thereof—that stimulation of the DLPFC has on metacognitive sensitivity [12–15]. Here, we propose an experiment that tests the effects of bilateral HD-tDCS of DLPFC on task performance and metacognitive sensitivity, while simultaneously investigating the effects of placebo on task performance and metacognitive sensitivity.

This project aims to advance the understanding of the placebo effect and its role in potentially interacting with metacognitive processes while simultaneously studying the effects of bilateral HD-tDCS of the DLPFC on task performance and metacognitive sensitivity and how stimulation of DLPFC possibly alters metacognitive sensitivity. **Our goals are to determine the effects of placebo on task performance and metacognitive sensitivity and determine the interaction between the placebo effect and metacognitive sensitivity. Our novel combination of electrical stimulation using a HD-tDCS montage and verbal expectancy cues to induce the placebo effect, that we will test using human participants, will aid in understanding the placebo effect, metacognitive sensitivity, and the interactions between the two.**

Aim 1: **Determine the impact of placebo on task performance and metacognitive sensitivity using type 1 performance (*d'*) and M-difference (*meta-d' - d'*).** Thus, we propose an experiment, using human participants, with the following criteria:

a. Participants will be given verbal expectancy cues during active test blocks where they are receiving electrical stimulation. Cue order is randomized and comes in three variants: positive, negative, and neutral.

b. Sham stimulation will be used as an experimental manipulation.

c. In order to identify which participants may be more susceptible to the placebo [16], participants will be instructed to fill out a questionnaire, containing the Interpersonal Trust Scale [17] and the Absorption Scale of the Multidimensional Personality Questionnaire [18–24].

Aim 2: **Determine the interaction between the placebo effect and metacognitive sensitivity when altering metacognitive sensitivity using bilateral HD-tDCS of the DLPFC.**

a. Pilot work modelling appropriate HD-tDCS electrode montages found a montage that maximizes current density in key regions of interest [12,25,26]: left and right DLPFC.

b. Use a visual perception task that requires participants to make judgements based on visual stimuli and report the level of confidence they had in those judgements.

c. Participants will undergo bilateral HD-tDCS of the DLPFC.

d. Baseline data will be collected for each session to ensure accuracy [27] and provide a solid comparison to the data collected from active stimulation test blocks.

>> BACKGROUND.

Here we intend to use noninvasive electrical stimulation and verbal expectancy cues to investigate and characterize the link between the placebo effect and perceptual metacognitive sensitivity in healthy human subjects.

Placebo Effect.

The **placebo effect** can be described as a set of positive changes that occur in response to a placebo treatment—one that has no actual therapeutic value—often paired with the context in which this treatment is administered [1]. Negative effects that can be caused by inert treatments are termed **nocebo effects** [1–3], but, for simplicity, we shall be referring to any effects caused by placebo treatments, positive or negative, as being a placebo effect unless specifically describing a nocebo response.

Expectations, of the subject and researcher alike, exert a strong influence on the strength of the placebo effect and have been shown to exacerbate subject responses to inert treatments [1–4]. These expectations can stem from personal experiences and beliefs, observational learning, and instructions or information received from researchers and other sources [3]. They can also develop from environmental cues in the experimental setting (e.g., clinical research being conducted in a medical setting, the

researchers wear lab coats, participants are given pills, etc.) [3,5]. Verbal instructions or suggestions, which will be utilized in this project, have been shown to play an important part in inducing placebo responses to inert treatments [5].

This psychobiological phenomenon is extremely relevant to researchers in a diverse range of fields and is often described as difficult to quantify [6]. The attempts that have been made are usually only done so in a clinical setting, such as when testing a new therapeutic method [7]. Some key limitations in the field are the difficulty in isolating the placebo effect from actual experimental results and the task of actually quantifying placebo [6,8].

Metacognitive Sensitivity.

Given the strength of the placebo effect in altering self-evaluative responses to inert treatments [9], it is reasonable to hypothesize that the placebo effect would also interact with metacognitive processes. **Metacognition** refers to higher-order cognition regarding active control and monitoring of cognitive processes surrounding learning, famously simplified to “thinking about thinking” [10,11]. Closely related is the idea of **metacognitive sensitivity**, which can be best described as the efficacy with which a participant’s accuracy and confidence are associated [11–13].

For example, if a participant is shown visual stimuli and instructed to discriminate the identity of the stimulus as well as give a confidence rating of their judgement, a participant with unimpaired metacognitive sensitivity would be able to indicate high confidence when choosing the correct answer and indicate low confidence when choosing an incorrect answer. If participants are instructed, via verbal expectancy cues, that some intervention they are receiving will affect their performance, then, due to the placebo effect, it is likely that their metacognitive judgements of their performance

should change accordingly, even if their task performance is not actually affected [11,14]. However, an open question remains regarding whether the placebo effect alters metacognitive sensitivity and, if so, how?

Target of Stimulation.

The **dorsolateral prefrontal cortex** (DLPFC) plays a role in higher-order cognitive functions such as working memory [15], decision making [16,17], and other important processes. Importantly, this region has been implicated as being involved in metacognition [11,18] and placebo [19]. For example, evidence indicates that DLPFC is integral for accuracy in terms of retrospective judgements of performance [11]. In response to placebo treatments, greater activation of DLPFC and other prefrontal regions has been observed, suggesting that prefrontal regions are involved in the representation of expectancy and other situational context surrounding placebo effects [20].

Additionally, noninvasive neural stimulation of DLPFC in humans has also been found to modulate the accuracy of working memory and retrospective self-evaluations of performance [21]. For transcranial direct current stimulation (tDCS) studies that look into subjects such as perception, attention, and memory, DLPFC is often targeted [22]. However, no studies have combined bilateral stimulation of DLPFC with a focus on metacognitive sensitivity, the placebo effect, and their possible interaction.

Stimulation Type.

We are going to use **transcranial direct current stimulation** (tDCS)—**a noninvasive form of neuromodulation**—to bilaterally stimulate DLPFC. Bilateral stimulation was chosen as there is a lack of consensus over the combination of which side of DLPFC and form of stimulation (anodal or cathodal) actually affects DLPFC processes [16,23–26]. Placebo effects are highly prevalent in studies that use tDCS to treat a

wide range of issues: depression [27], pain [28], addiction [26,29], motor learning [30], memory [31], and many more. In comparison to transcranial magnetic stimulation (TMS), tDCS is much less diffuse and the stimulation is often not as obvious to the subject as TMS, making it harder to study placebo using the former technique [32]. Additionally, the capability of a customizable sham form of stimulation that is available when using tDCS makes it the optimal method of neurostimulation in this experimental design.

High Definition Transcranial Direct Stimulation (HD-tDCS).

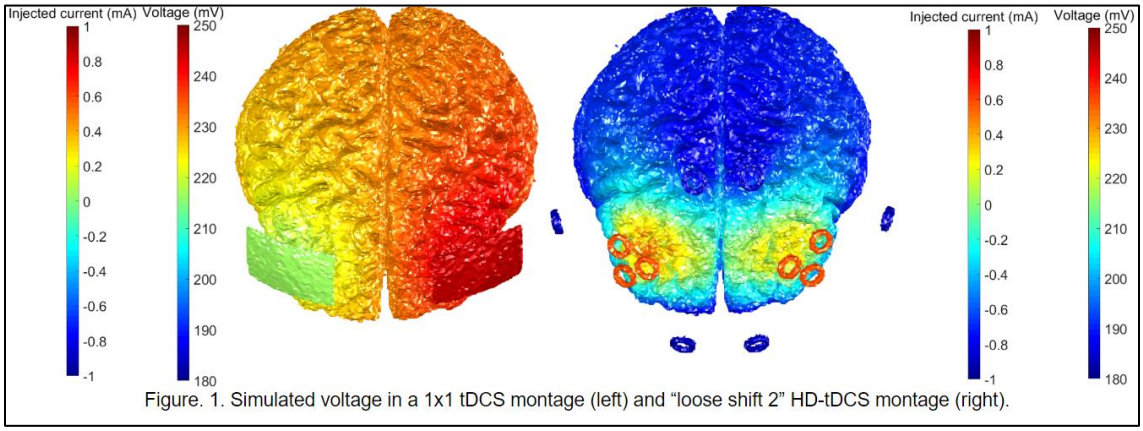

Figure. 1. Simulated voltage in a 1x1 tDCS montage (left) and "loose shift 2" HD-tDCS montage (right).

Here, we will be using a **HD-tDCS** montage in lieu of the large sponge electrodes typically seen in standard 1x1 tDCS, where there is one anodal electrode and one cathodal electrode. The usage of HD-tDCS provides **focalised stimulation** and offers better control of which cortical regions are being most affected by electrical stimulation compared to traditional tDCS which typically stimulates larger regions of the cortex with subpar spatial precision [33]. Due to the ring structure, rather than just a single large sponge pad, the stimulation penetrates further and with greater focus in the region of interest [34]. Additionally, the ring radius can be adjusted inwards and outwards as well as be rotated to provide greater spatial and polarity control. During the montage modeling portion of this project, we observed more targeted stimulation in our HD-tDCS montage in lieu of the more diffuse stimulation seen in standard 1x1 tDCS (Fig. 1).

Similarly, the simulations of the electric field showed better stimulation focality and a higher electric field in key regions with HD-tDCS rather than 1x1 tDCS (Fig. 2).

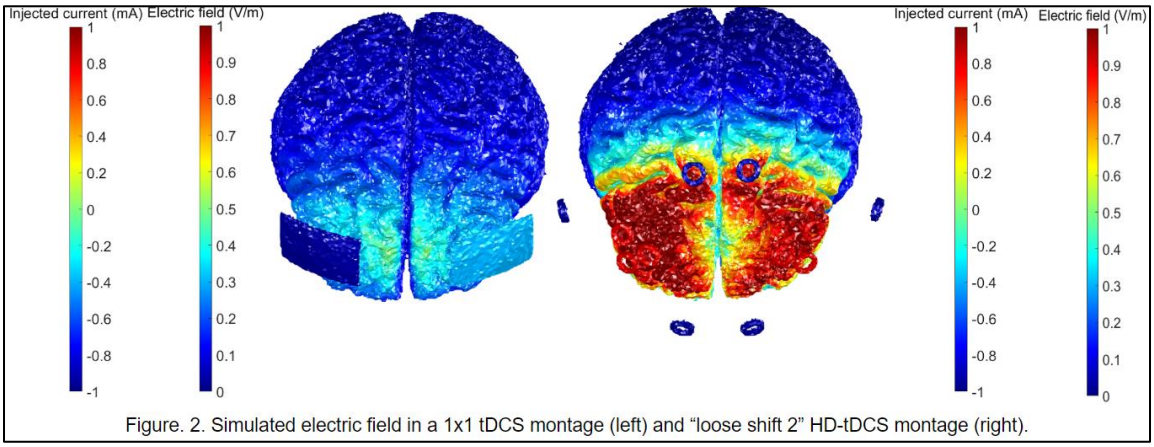

Figure. 2. Simulated electric field in a 1x1 tDCS montage (left) and "loose shift 2" HD-tDCS montage (right).

While there is a concern over the focalized stimulation causing thermal injuries to the scalp, this form of stimulation has been shown to cause negligible changes in skin temperature [35] and prolonged, repeated cortical stimulation using HD-tDCS has been shown to be safe [36]. Additionally, as a final safety measure, we will be running an impedance check before turning on the stimulation; this is to ensure that all the electrodes are gelled correctly and that there is stable conductivity so as to reduce discomfort. The method that we will be using has been **IRB-approved,** and participants are notified each session of any possible discomforts that may occur due to the stimulation. They are also reminded that they may leave at any time and instructed to alert us if the stimulation becomes painful so that we may safely shut it off.

With this project, we aim to study the main effects and interaction of the placebo effect and metacognitive sensitivity by using HD-tDCS, a placebo-prone device, to bilaterally stimulate DLPFC, using active and sham stimulations and having subjects participate in a behavioral study while being given verbal expectancy cues.

>> SIGNIFICANCE.

The placebo effect is a well-known psychobiological phenomenon that is well-documented and ubiquitous in research but often not quantified. When it is measured, it is often only done so in clinical settings, such as drug trials [7]. With our experimental setup, we aim to not only quantify placebo through the counterbalancing of each standard experimental parameter but also study if and how the placebo effect potentially alters metacognitive sensitivity. There is a clear clinical significance to studying the interaction of the placebo effect and metacognitive sensitivity. In a clinical setting, whether it be experimental or otherwise, healthcare professionals and experimenters alike rely on a patient's self-reporting capabilities. If, due to a placebo treatment, that personal assessment capability is altered, how does that affect future involvement in the study/treatment program and the patient's response to an active treatment if one is relying on self-reporting? While metacognitive sensitivity and the placebo effect are of clinical interest separately, the interaction of the two is of clear importance.

The broader implications of an interaction between the placebo effect and metacognitive sensitivity could have a potentially crucial significance to clinical care and treatment guidelines. A patient who has lowered metacognitive sensitivity, such as individuals diagnosed with dementia [37] or schizophrenia [38], could be more susceptible to placebo. If this individual is more susceptible to a placebo then how does this affect informed consent and their response to any treatment that they will receive? How will their self-reporting capabilities be considered by the researcher/clinician, will they continue to receive treatment, and will this treatment be active or placebo? This subject also raises the question of how to ethically treat someone who has lowered metacognitive abilities and/or whose metacognitive capabilities are affected by placebo.

A point of contention preexisting in the field is the relationship between informed consent and placebo treatments; some researchers have pointed out that a lack of explanation given to participants regarding understandable descriptions of the role of placebos and their functions in an experiment breaches the ethical obligations of the researcher [39]. How can a participant give informed consent if they have not been fully informed of key aspects of the experiment such as possible placebos and their effects? A greater understanding of not only how the placebo effect may alter task performance and metacognitive sensitivity but also the interaction it may have with metacognitive sensitivity could shed light on this dilemma.

Additionally, the usage of bilateral HD-tDCS will contribute to an ongoing debate over whether or not stimulation of DLPFC can affect metacognitive performance [14,40–42]. This project builds upon these previous studies by using HD-tDCS and montage modeling to more accurately target and stimulate DLPFC in order to effectively study what effect neuromodulation of DLPFC has on task performance and metacognitive sensitivity.

>> INNOVATION.

This project is innovative in several respects. The combination of bilateral HD-tDCS of DLPFC and verbal expectancy cues during a behavioral task is novel and allows us to study the placebo effect, metacognitive sensitivity, and any interactions between the two. For the behavioral portion of this project, we will be studying the interaction of the placebo effect and metacognitive sensitivity as well as the effect of bilateral HD-tDCS of DLPFC on the placebo effect and metacognitive sensitivity. This combination of the above points of focus and the usage of montage modeling to find an optimal HD-tDCS montage is also novel and will allow us to better target DLPFC in order

to potentially alter metacognitive sensitivity and the placebo effect. In terms of the analytical portion of this project, signal detection theory (SDT) analysis methods will be applied to the placebo effect [12,13]. Type 2 SDT including metacognitive sensitivity will be applied to the placebo effect, allowing us to quantify placebo and determine its interaction with metacognitive sensitivity in our experimental paradigm. These experimental methods and points of focus are not only novel in their combination but will provide valuable information and potentially encourage future studies using similar experimental methods.

>> APPROACH.

Overview and Motivation.

There is still a significant lack of knowledge surrounding the placebo effect and its effect of metacognitive sensitivity. However, there is an indication of possible association between the two due to evidence that placebo treatments can exert influence on self-evaluations as opposed to sensory sensitivity [43].

Based on this, we can hypothesize that placebos will interact with metacognitive processes. A positive verbal expectancy cue (i.e., “This stimulation ought to make you perform better.”) may cause participants to become more confident in their choices without any significant changes in task performance; essentially, metacognitive sensitivity is being affected through the generation of specific metacognitive biases [13]. This phenomenon has previously been observed in placebo analgesia studies where participants need a more intense stimulus to make the appropriate pain judgments after receiving a placebo treatment [11]. Additionally, there is also the possibility that the placebo effect will alter task performance. Several placebo analgesia studies have found—to differing degrees—decreased pain-based brain activity

in regions containing nociceptive neurons [9]. It is reasonable to assume that decreases/increases in neural activity of a cortical region such as DLPFC could alter task performance. Additionally, we expect that the strength of the placebo effect will differ on a subject-by-subject basis. It is widely documented that certain people exhibit a greater predisposition to placebo treatments and expectancy effects [7]. However, due to the complicated nature of the placebo effect, it is difficult to predict what may or may not occur with any degree of certainty.

We hypothesize that bilateral neuromodulation of DLPFC will alter metacognitive sensitivity. However, based on previous studies, it is difficult to say with certainty what effect will occur. One possibility is the "anodal-excitatory, cathodal-inhibitory" (AeCi) hypothesis where anodal stimulation will cause an excitatory response (i.e., increase in task performance due to excitation of this neural region) and vice versa [44]. While this hypothesis holds true for motor regions, it is rarely applicable for cognitive regions such as DLPFC [44]. While anodal stimulation can cause an excitatory response, cathodal stimulation rarely causes inhibition. This could be due to several factors: the more richly connected networks observed in cognitive regions, the initial level of activity of the stimulated area, and bilateral compensation of cognitive regions where any Ci effect may be compensated by the non-stimulated hemisphere. We will hopefully counter the latter possibility by bilaterally stimulating DLPFC. One may even observe an "anodal-inhibitory, cathodal-excitatory" response in cognitive regions; this could be due to an increase or decrease in neuronal competition, reducing or improving task performance. Finally, we may observe no changes in task performance or metacognitive sensitivity due to bilateral HD-tDCS of DLPFC. This could be due to homeostatic plasticity, a form of neuronal self-regulation where deviations of neural activity from baseline are

corrected, preventing alterations of baseline firing rate, which has been previously observed in motor cortex [45].

Experimental Design.

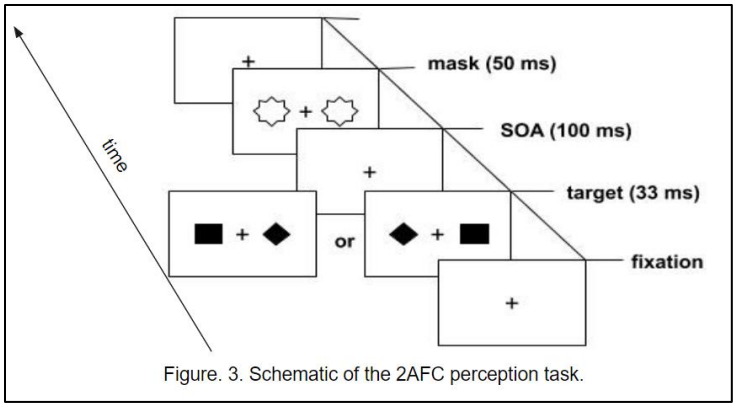

Figure. 3. Schematic of the 2AFC perception task.

The **behavioral task** (Fig. 3) that we are going to use is a visual two-alternative forced choice (2AFC) perception task that has been utilized previously and shown to be effective when studying metacognitive sensitivity [14,40]. We slightly modified the confidence response to better distinguish confidence levels. The original task had participants answer either "clear" or "unclear"; this was adjusted to a **1-4 confidence scale**, with one being indicative of simply guessing which orientation the participant saw and four indicating that the participant is sure that their choice is correct. The projected stimuli will be shown for 33 ms and have sides equivalent to 0.8° of visual angle, centered 1° to either side of the crosshair. A metacontrast mask is displayed for 50 ms, 100 ms after stimulus onset, to increase task difficulty. The two possibilities (diamond right/square left and vice versa) have an equal probability of being presented and are arranged in a pseudorandom order. Participants will be tasked with judging the spatial arrangement of the stimuli presented while simultaneously giving a confidence rating of their choice. Blocks of 300 test trials each will be preceded by a short practice block and at least one threshold block to adjust the metacontrast mask. The threshold task was designed with two interleaved staircases: A and B. Staircase A was designed as a one-up-two-down staircase, making it the more difficult staircase, while B is a one-up-three-down design, making it the easier staircase. The cumulative task performance

of trials using staircase A is designated “percent correct high,” while the task performance of trials using staircase B are denoted as “percent correct low”. Task difficulty will be adjusted to each participant to achieve 71% and 79% task performance, in staircases A and B, respectively [46]. Testing will be done in a dark, sound-attenuated room, with stimuli presented, using MATLAB, on a NEC MultiSync FE2111SB 21” monitor with a refresh rate of 75 Hz. Each subject will have their chin resting on a chin-rest approximately 43 cm away from the screen.

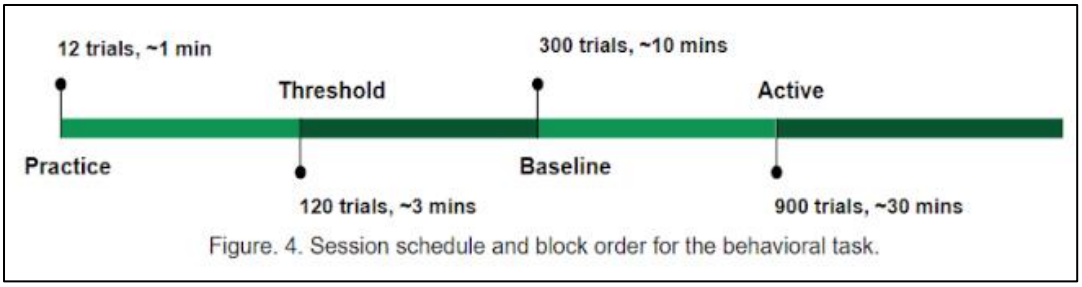

Figure. 4. Session schedule and block order for the behavioral task.

Participants will attend three testing sessions over three days, with 1.5 hours of testing per session. Participants will undergo one type of stimulation (anodal, cathodal, or sham) per test session, and the order in which they receive these types of stimulation is randomized. They will be given verbal expectancy cues while never knowing which tDCS stimulation they are receiving. Each test session consists of a series of practice, threshold, baseline, and active trials (Fig. 4). The practice block is used to get the participant’s eyes adjusted to the dark and allow them to get comfortable with the task; this is an extremely slowed down version of the task that provides feedback on their performance. On each day of testing, all subjects will perform at least two threshold blocks to adjust the metacontrast mask; this threshold block is conducted each session to account for learning effects. **Baseline testing**, with no stimulation or verbal cues given, will be conducted daily to account for day-to-day differences in subjects’ baseline performance due to learning effects or other factors [47]. Finally, the participant will

complete three active test blocks where they receive electrical stimulation and verbal expectancy cues (cue order is randomized).

Pilot data: The behavioral task was shown to be effective and produce reliable results when tested. Ten participants were recruited (7 female) and instructed to complete two rounds of testing consisting of at least two threshold blocks and two test blocks (Fig. 3), in each round. Task performance was recorded as percent correct, low and high, for each test block (labeled Test 1 or Test 2).

To analyze the data and see if task performance was stable, we looked at the within subjects main effects and interaction via a **repeated measures ANOVA** with two factors: test block (1 or 2) and task difficulty (low or high), as set by staircases A and B in the threshold block of the task. Task performance did not vary significantly as a result of the test block number, $F(1, 19) = 0.993$, $MSE = 43.90$, $p = 0.331$, but did vary significantly based on task difficulty, $F(1, 19) = 14.159$, $MSE = 153.51$, $p = 0.001$. The latter result is expected since participants are performing the behavioral task under two different difficulty levels, one easier and the other more difficult, resulting in an expectedly significant difference in task performance. The former measure, test block 1 and 2, provides a more interesting result as there are no significant differences in performance between test blocks, and the participants' performance doesn't dramatically change from one test block to the next, indicating that the behavioral task produces reliable results. Furthermore, there is no significant interaction between test block and task difficulty, $F(1, 19) = 1.304$, $MSE = 18.09$, $p = 0.268$, showing us that even though there are significant differences in task performance due to changes in task difficulty,

these differences do not significantly interact with the test blocks to dramatically alter task performance.

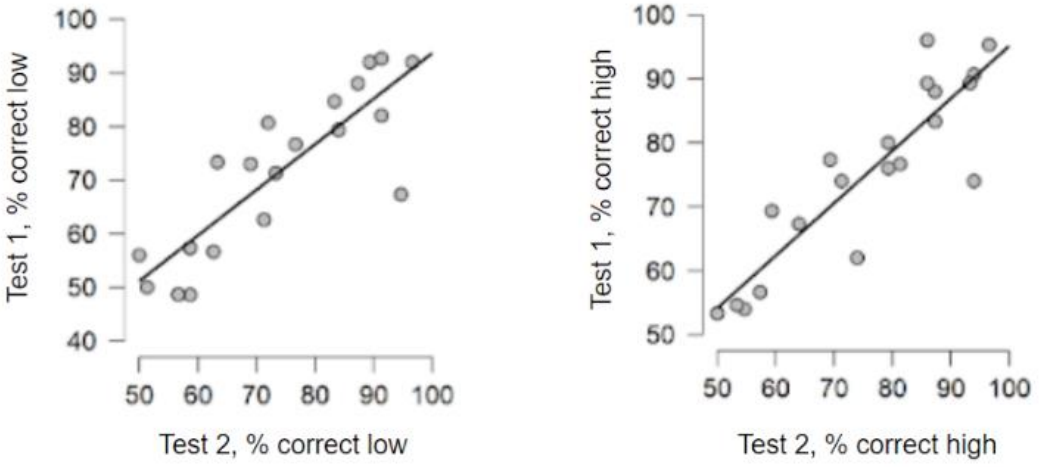

Figure. 5. Scatterplots showing relationship between Test 1 and Test 2 for percent correct low and high.

We also conducted correlation tests to study the association between the test blocks for percent correct low and high and also created scatterplots where Test 1 was plotted on the x-axis, Test 2 was plotted on the y-axis, and each dot represented a test round (with two rounds being assigned to each of the ten participants for 20 data points in total). The scatterplots of percent correct low and high (Fig. 5) seemed to show correlation between the two, and this can be confirmed or denied using a **Pearson's correlation test**. The first correlation test of Test 1 versus Test 2 percent correct low showed significant correlation, $r = 0.850$ and $p < 0.001$, as did the second correlation test of Test 1 versus Test 2 percent correct high, $r = 0.888$ and $p < 0.001$. Both P-values were less than 0.001 so we can conclude that Test 1 and Test 2 are linearly associated, which matches what is observed if the data are plotted (Fig. 5).

The repeated measures ANOVA and correlation tests both demonstrate the **robustness and test-retest reliability of the behavioral task**. There are no significant differences in task performance based on test block, indicating consistent task

performance from the participants when doing the task, and there is a linear association between Test 1 and Test 2, showing that both are in agreement and that there are no major indications that there are problems with the task that can influence data collected in the main experiment.

The pilot data also provided valuable insight into the experimental proceedings. From these ten participants, we learned that the threshold task has to be run at least twice in order to get an appropriate adjustment of the metacontrast mask to allow participants to get used to the speed of the task and make the test blocks suitably difficult. Exclusions based on task performance were also put into the experiment's procedure; anyone who routinely scores below 60% or above 90% during a session are now considered to be performing outside of the experiment's response criteria since they are essentially at floor and ceiling, respectively, for task performance and monitoring significant changes in their task performance would be difficult.

Montage Modeling.

Pilot work: Simulated electrode montages exhibit varying levels of current density in regions of interest: right and left DLPFC. **Montage optimization** was done to maximize current density in the regions we were interested in stimulating: right and left DLPFC. This was done using ROAST [48,49] in MATLAB along with the SPM12 toolkit to virtually map electrode positions onto a segmented head, generate a FEM mesh, and solve for voltage and electrical density before pushing the estimated tDCS voltage output to MNI space.

The **realistic volumetric-volumetric approach to simulate transcranial electric stimulation (ROAST)** offers a complete fully automated, open-source pipeline [48,49]. Transcranial electrical stimulation (TES) modeling prefers volumetric finite element

models (FEM) to better represent anatomical morphology, and ROAST has been shown to produce accurate, reliable simulations using these models. This program processes individual MRI volumes to generate 3D renderings of resulting current and electric field distributions based on various inputs in a fast, automated fashion. The ROAST pipeline contains the following components: segmentation, electrode placement, finite element meshing, and FEM-solving. The segmentation algorithm is found in the SPM12 toolkit and is applied to the head and neck to ensure continuity and anatomical accuracy when modeling a human head. Electrode placement allows the user to model electrode montages from a variety of EEG systems such as the 10-20 and BioSemi-256 EEG systems. MATLAB toolboxes are used to generate a finite element mesh that is fully customizable; FEM-solving uses an open-source solver to solve the Laplacian equations with the user specifying current coming in and out of each electrode and various tissue conductivities. 3D renderings are then generated of the current and electric field distributions. When compared to preexisting pipelines and software, ROAST provides

	MNI Coordinates			
Node	*x*	*y*	*z*	BA
Left anterior PFC [46,47]	-20	53	12	10
Right anterior PFC [46,47]	33	50	9	10
Right anterior PFC [46]	24	65	18	10
Right DLPFC [46]	36	39	21	46
rhDLPFC [36]	37	26	50	8
lhDLPFC [36]	-41	18	52	8

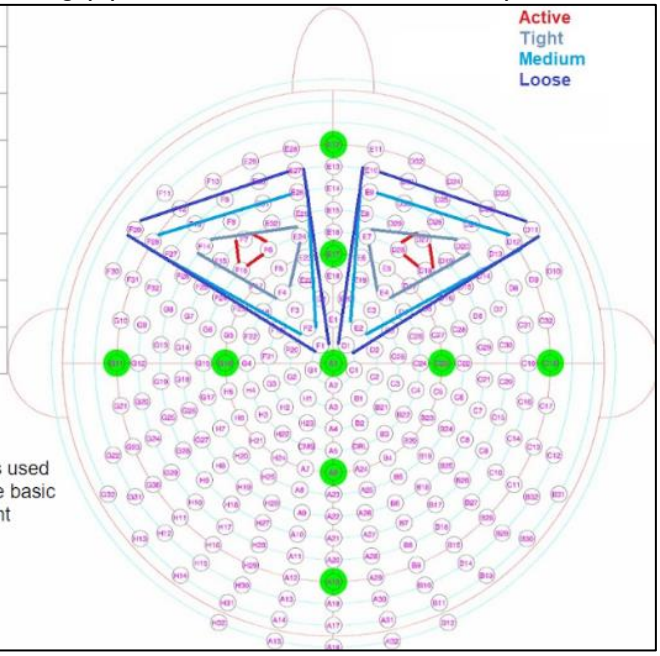

Figure. 6. A table of MNI coordinates for the key regions used in montage modeling and a BioSemi-256 system with the basic electrode montages. BA = Brodmann area, rh = right hemisphere, lh = left hemisphere.

accurate simulations in a much faster, user-friendly way without the need for multiple pipelines and software packages.

The MNI coordinates and Brodmann areas (BAs) of key regions (i.e., regions shown to be important to metacognitive sensitivity) (Fig. 6) were taken from literature [14,50,51], and current densities were plotted across these regions in order to see which montage maximized current density while targeting these regions of interest (Fig. 6). The active electrode positions were kept constant in the right and left hemispheres: D27, D28, D18 and F7, F6, F16, respectively [14]. The reference electrodes were broken up into three, broad montages: “tight”, “medium”, and “loose”—based on the BioSemi-256 system (Fig. 6). They were then further divided by adjusting these three montages via rotating or flipping them to achieve different configurations (Fig. 7). Based on the montage comparisons (Fig. 7), the two best montages for maximizing current density were “loose” and “loose shift 2,” and the latter was chosen. The montage, **“loose shift 2”**, was shown to maximize current density in key regions in right and left DLPFC as opposed to anterior PFC which we are not as interested in as DLPFC is the focus of this project.

Montage	Right hemisphere	Left hemisphere
Tight	D20, E7, E4	F14, E24, F4
Tight shift 1	D26, E6, D5	F8, E23, F23
Tight shift 2	D30, D4, D15	E31, F18, F25
Tight shift 3	D20, E6, D15	F8, E23, F25
Tight shift 4	E4, D20, D30	F4, F14, E31
Tight shift 5	D26, E7, D16	F24, F8, E24
Medium	D12, E9, E2	F28, E26, F2
Medium shift 1	D21, E8, D3	E25, F13, F19
Medium shift 2	D24, E6, C28	E23, G6, F10
Medium shift 3	D31, D7, E20	E21, G8, E30
Loose	D11, E10, D1	F29, E27, F1
Loose shift 1	E20, C30, E11	E28, E21, G13
Loose shift 2	E2, D8, E11	E28, F32, F2

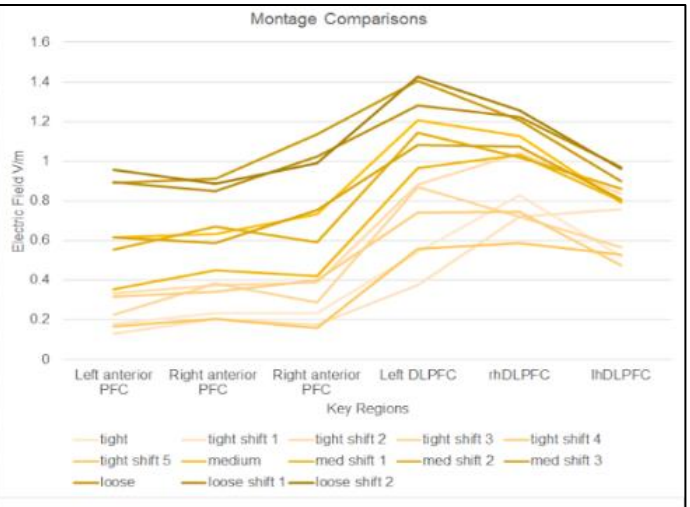

Figure. 7. A table of montages tested and a graph plotting the current densities of the montages across the key regions.

The tDCS will be done using a **NeuroMod tXES** device, a noninvasive method to deliver electrical stimulation to the brain. The device included a software package of MATLAB files that allowed us to create customized tDCS files. Based on preliminary research and literature, we decided to have stimulation be set at 0.66 mA per electrode for about thirty minutes. Since each hemisphere will have a total of three electrode pairs (active and reference) the stimulation to right and left DLPFC will be ≤2 mA on each side, for ≤4 mA total, which has been IRB-approved and shown to be safe [52,53]. Also, based on pilot data, **this stimulation has been shown to be tolerable**, and participants are regularly reminded that they may stop and leave the study at any time due to discomfort from the stimulation. We will be using ring electrodes; the anodal electrodes will always be placed in the "active" electrode configuration while the cathodal electrodes will be always placed as "reference" electrodes. Due to this positioning, we created three tDCS files using the provided software: anodal, cathodal, and sham stimulation. Anodal and cathodal stimulation were set at twenty-nine minutes of stimulation at 0.66 mA and -0.66 mA, respectively, with a ramp-up and ramp-down of thirty seconds. This ramp allows for participants to adjust to the stimulation and gives them time to let us know if the stimulation is at all painful. The sham file has a thirty second ramp-up to 0.66 mA followed by an immediate ramp-down to 0 mA [54]. Since we are using a HD-tDCS montage, stimulation is noticeable and a sham stimulation of just 0 mA for thirty minutes would be extremely noticeable and ruin the whole point of having participants undergo sham. As the participants experience stimulation for the thirty minute period, the sensation can fade and this phenomenon has been recorded in most participants in the pilot data group. Thus, this form of stimulation with only a ramp-up and ramp-down is appropriate for a sham stimulation.

Pilot data: Data was collected from participants who went through the entire experimental design, and we received valuable feedback. **Active data collection** had already begun, and usable data had been collected from three participants: two of these participants completed all three sessions while the third only completed two sessions. Other participants were either excluded based on performance or voluntarily left the study. However, due to the **COVID-19 pandemic**, all human subjects research was halted, and data collection could no longer continue. While this was unfortunate, we had gained a significant understanding in how our experiment was perceived by participants, learned useful information, and received interesting feedback from most of the participants. Additionally, since we had already started data collection, an experimental procedure has already been written up and revised that can be used for future data collection.

Questionnaire.

To account for confounding variables, participants will be asked to complete a questionnaire at the end of their final session, and female participants will be asked to provide information about the date of their last menstrual cycle.

The latter is to account for changes in cortical excitability that occur due to changing levels of ovarian hormones related to the menstrual cycle [55,56]. We will categorize the self-reported menstrual cycle data into three levels: early follicular phase (F1), late follicular phase (F2), and luteal phase (L). In F1 (days 1-6 after onset of last menses), estradiol levels and progesterone levels are typically low, estradiol levels rise in F2 (days 7-12) while progesterone remains low, and both estrogen and progesterone levels are usually high in L (days 14-28). Inhibition has been found to be associated with

higher levels of progesterone while the converse is true for estradiol levels, seeing greater levels of estradiol leading to excitation [56].

The questionnaire will be used to measure a participant's susceptibility to the placebo effect. It consists of two parts: the Interpersonal Trust Scale [57] and the Absorption Scale of the Multidimensional Personality Questionnaire [58–64]. The Interpersonal Trust scale is a 25-item scale where each item is rated on a scale of 1-5, and the Absorption Scale is a 34 true/false-item subscale. The Interpersonal Trust Scale is more complex as each item is scored on a 1-5 scale of "strongly agree" to "strongly disagree." Scores can thus range from 25 (lower trust) to 125 (higher trust) with a neutral midpoint of 75. Those who score higher on the Absorption Scale (i.e., choose "true" more often) have been found to be more susceptible to the placebo effect [7], and it is thought that the same will apply to those who score as "more trusting" based on their answers to the Interpersonal Trust Scale.

Behavioral Measures.

We will be looking at how the experimental manipulations of various types of stimulation and verbal expectancy cues affect type 1 performance and type 2 performance (i.e., task performance and metacognitive sensitivity or *d'* and *meta-d'*). Signal Detection Theory (SDT) analysis will be used to estimate metacognitive sensitivity using ***meta-d'*** [12]. This is an estimation of the amount of signal available for performing the confidence/visibility task. Type 2 performance (*meta-d'*) will be directly compared to ***d'***—the signal available for the primary stimulus identification task—using the M difference: *meta-d' - d'*. Type 1 performance (*d'*) only takes into account how well the participant discriminates between stimuli, while type 2 performance (*meta-d'*) takes into account how well the participant's judgements align with their confidence ratings of said

judgements (i.e., does the subject rate themselves high confidence for correct answers and low confidence for incorrect answers). This value of type 2 performance is found by performing similar SDT calculations as one would for calculations of type 1 performance, taking into account the accuracy of a subject's judgements along with the confidence assigned to those judgements [12,13]. MATLAB code has also been written that implements this analysis of *meta-d'* [12]. Since type 1 and type 2 performance are intrinsically linked, metacognitive performance has to be normalized to task performance using the **"M difference"** (a SDT measure of metacognitive sensitivity that is free of bias), *meta-d'* - *d'*, to account for subject differences in task performance [14]. If *meta-d'* < *d'*, some signal that is available for primary stimulus identification is absent for metacognition, indicating a loss in metacognitive sensitivity. If there is no effect of tDCS or placebo on metacognitive sensitivity *meta-d'* should equal *d'* or at least be not statistically different (minor differences can be caused by noise and other factors).

Statistical Analyses:

Statistical analyses of Aims 1 and 2 will be addressed by a omnibus **three-way, repeated measures multivariate analysis of covariance (MANCOVA)**. This omnibus MANCOVA will have a three-way factorial design, where the three factors—stimulation, verbal cue type, and task difficulty—and their interaction will be evaluated in terms of type 1 performance and the M difference (i.e., type 2 performance (*meta-d'*) - type 1 performance (*d'*)); both of these measures will have baseline measurements subtracted from them to account for changes in baseline performance [47]. Task difficulty will be included as a factor in order to prevent artificial inflation of metacognitive sensitivity during our statistical analyses [65]; thus, the results of the two staircases, A and B (denoted as "high" or "low" task difficulty, respectively) will be analyzed separately. The

concomitant variables are the results of the questionnaire and the menstrual cycle data collected from female participants.

This three-way, repeated measures MANCOVA will study the main effects and interaction of the three verbal expectancy cues (better, worse, and no effect) and the three types of HD-tDCS (anodal, cathodal, and sham) along with task difficulty (low or high). The concomitant variables allow us to account for possible confounding or lurking variables. In order to account for baseline performance, all measures will be normalized by subtracting the baseline measures from their counterpart to account for day-to-differences in performance and learning effects [47]. Accounting for baseline performance and metacognitive sensitivity allows us to account for learning effects and to examine any changes from baseline that occur, which are of particular interest to us.

>> Aim 1: Determine the impact of placebo on task performance and metacognitive sensitivity using type 1 performance (*d'*) and M-difference (*meta-d' - d'*).

The placebo effect will be triggered via verbal expectancy cues; these cues come in three forms: better, worse, and no effect (e.g., "This stimulation ought to make you perform better/worse at the task." or "This stimulation ought to have no effect on your task performance."); cue order will also be randomized. We also have the visual aids of a lab coat that the researcher will wear throughout the experimental session and the lab setting in and of itself which will potentially trigger a placebo effect in the participant; the usage of environmental cues has been previously noted to trigger expectancy effects [2,4,66]. Before each test block, the researcher will come into the treatment room and give the appropriate verbal cue before leaving the room and starting the respective behavioral task test block.

Figure. 8. Plots of (left to right) d', meta-d', and M difference and average confidence for low and high task difficulty for all subjects across the three stimulation types (Cathodal, Anodal, and Sham) and verbal cue type (Better, Worse, and No Effect).

Data collected from Subjects 2, 4, and 5 show that while our analyses are working, the effect is messy, and no clear trends are observed (Fig. 8). From these pilot data, we decided that for all future data collection, the threshold task will be run daily instead of only during the first session in order to counter learning effects that were observed in all three participants. We also will, in the future, have the combinations of stimulation types and verbal cues arranged in a pseudorandom order to counter any ordering effects. This means that every participant will have a different combination of stimulation types and verbal cues to ensure an equal distribution of all possible combinations.

Since only Subjects 2 and 5 completed all three sessions, they were the only ones to complete the questionnaire containing the Interpersonal Trust Scale [57] and the Absorption Scale of the Multidimensional Personality Questionnaire [58–64]. Subject 2 scored 80 on the Interpersonal Trust Scale, and this would indicate that Subject 2 is more trusting. However, Subject 5 had a more neutral level of trust, scoring a 67. They

scored 33 and 28 on the Absorption scale, respectively; this indicates that they are more likely to be susceptible to the placebo effect [7]. Based on their data, we observed no significant effects caused by placebo, but this is most likely due to the lack of data available.

>> Aim 2: Determine the presence and strength of any possible interactions between the placebo effect and metacognitive sensitivity while attempting to alter metacognitive sensitivity via bilateral HD-tDCS of DLPFC.

To prevent researcher bias, stimulation order was randomized for each participant and **blinded** files were created of these stimulation types, personalized per participant and session. For example, if randomization of "Subject 1's" stimulation order resulted in them undergoing cathodal, anodal, and sham stimulation for their three sessions, respectively, then copies of the stimulation files would be made and appropriately named using the following convention: "Subject1_Session1", Subject1_Session2", and Subject1_Session3". As these files are all generated beforehand, the researcher does not know which form of stimulation the participant is receiving, reducing researcher bias and expectancy effects [2,4].

Participant comfort and safety is of the utmost importance, and they are regularly informed that they are free to leave at any time without any repercussions and are to notify us immediately if the stimulation becomes at all painful. For this purpose, a **webcam** has been set up in the treatment room that allows us to monitor the participant at all times. Should they have any questions, be experiencing pain or discomfort, or wish to stop, they simply motion for us to come in and we immediately enter the room. From the participants who have already undergone stimulation, the vast majority have found it to be tolerable and many have taken advantage of the webcam to let us know if they had

any questions or were experiencing issues. Only one participant left the study due to the stimulation being too strong for them.

No significant main effects or interactions of stimulation, verbal cue, or task difficulty were observed but this was expected as we do not have anywhere near the amount of data necessary to perform meaningful statistical analyses. The pilot data that we collected showed us the feasibility of this project, how it is received by participants, and helped us modify portions of the experiment.

>> Statistical Power.

In order to determine what sample size would be sufficient to detect a small effect size, f = **0.2**, we conducted an *a priori* power analysis. Due to the complexity of the MANCOVA analysis that will be used to analyze the data collected, we used a simpler test to determine the sample size appropriate when using extremely conservative values. Using G*Power [67,68], a **one-way, repeated measures ANOVA power analysis** was used with an α of 0.05 and a power (1 - β) of 0.95. It consisted of one group—meant to stand in for either stimulation or verbal cue type—with three measurements which represent the three types of stimulation and verbal cues used in this experiment. From this analysis, it was found that 66 human subjects are required to achieve this conservative power level. This estimation would be suitable to determine the main effect of just one factor: stimulation, verbal cue type, or task difficulty. To account for multiple factors, we propose increasing the sample size to **100 human subjects** in order to detect the main effects and interaction of our three factors.

>> Limitations and Other Considerations in Both Aims.

A major consideration of this project is how do we know that we are inducing a placebo effect during our experimental sessions? We would argue that, based on

previous studies [11,13,43] and the collection of average confidence ratings for each participant (Fig. 8), it is likely that the participants will alter their confidence ratings based on the verbal cues even if their task performance remained unaffected. This is a strong indication that the participants' **perception of their performance** could be affected by the verbal expectancy cues, showing that they are experiencing the placebo effect. While it is certainly very likely that some of the participants that we recruit will be nonresponders, it is also possible that these cues will have an effect on participants' perceptions which is the whole point of the verbal cues.

A notable limitation is that the montage modeling we did in order to find the appropriate montage, while extraordinarily useful, was not **subject-specific**. In order to conduct subject-specific montage modeling we would need individuals MRIs for each participant. However, previous studies relying on montage modeling using single heads **generally corroborate** the results of studies that used multiple MRI-derived models [69]. Additionally, MRI-derived individual head models are expensive to generate and we found it to not be necessary for this particular project. Subject-specific modeling could be utilized in our study if deemed appropriate and is a valid avenue of exploration for this study and future studies.

There are also possible concerns regarding the strength of the stimulation when using the HD-tDCS montage. While this form of stimulation and the level of stimulation that we are using has been shown to be **safe and tolerable** [52,53], it is also noted that the ring configuration of HD-tDCS can result in a stimulation that feels stronger as it is more focused than the 1x1 tDCS montage. Of the five participants who underwent HD-tDCS only one participant left the study due to the stimulation being too strong for them. If this level of stimulation resulted in more participants leaving the study we would have an

argument for lowering the stimulation, but this has not been the case thus far. Additionally, this form and level of stimulation has been IRB-approved. So the stimulation shall remain as is for now, unless we receive evidence indicating that the stimulation is too high.

>> Value of Negative Findings.

Even if our hypotheses are not supported, these data will still be informative.

The placebo effect does not significantly alter task performance or metacognitive sensitivity. If placebos have no effect on metacognitive sensitivity then this is of great value, clinically. This means that a patient's metacognitive sensitivity during self-reporting is not altered by placebos, indicating that they are able to self-evaluate accurately. This finding also opens up subjects for future studies. For instance, is this negative finding upheld in cases where an individual has a neurological disorder that lowers metacognitive sensitivity; will the placebo effect interact with metacognitive sensitivity in cases where a person is already experiencing a loss of metacognitive capabilities? Also, could it be that we simply recruited people who don't respond very strongly to placebo? It could be that the verbal expectancy cues we utilized simply weren't strong enough to induce a significant placebo effect. Altering the experimental design to include a stronger placebo, like those seen in clinical studies and placebo analgesia studies could result in observable changes in task performance and metacognitive sensitivity and is a valid course for future studies.

Bilateral tDCS of DLPFC does not significantly affect task performance or metacognitive sensitivity. If we observe no significant changes due to stimulation, we will still be gaining valuable insight into metacognitive sensitivity and placebo. These findings could back one side of the debate over whether or not stimulation of DLPFC alters

metacognitive sensitivity [14,40–42], and these negative findings can be explained in various ways as this conclusion has been anticipated, indicated by our various examples of what effects we may observe. This study does not mark the end of this debate, instead offering up more data to be analyzed and providing more questions for future studies.

>> Timeline.

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