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Sydney N. Haberberger
University Honors Program, syd8694@siu.edu

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Sydney Haberberger

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Sydney Haberberger, David G. Gilbert, Ph.D.

Southern Illinois University at Carbondale

Correspondence concerning this article should be addressed to David G. Gilbert, Department of Psychology, Southern Illinois University, Mailcode 6502, Carbondale, Illinois, 62901-6502. Electronic mail may be sent to dgilbert@siu.edu.

*To whom correspondence should be addressed.

David G. Gilbert, Ph.D.

Department of Psychology

Southern Illinois University

Carbondale, IL 62901-6502

e-mail: dgilbert@siu.edu

Abstract

The current study tested the hypothesis that the effects of THC on affect are mediated by the ability of THC to alter attentional bias to positive and negative stimuli. The study was completed by 16 participants, all of whom were consistent marijuana users. During sessions, participants used a machine called a Quantified Smoke Delivery System, which delivers a controlled amount of smoke to the user, to smoke either a cigarette that contained THC or a placebo cigarette. After smoking, participants would complete a task. During tasks, participants were placed in an eye tracking apparatus in order to record the movement of their eye gaze using an eye tracking program while they looked at a computer monitor. Participants were presented with sets of two pictures depicting faces showing varying degrees of different emotions and instructed to look freely between the pictures. Participant eye-gaze was then analyzed. A clear interaction between time and drug type was found, such that the eye-gaze of participants was biased more toward the negative emotional picture during the first .667ms of gaze time. A greater bias for positive relative to negative and negative relative to neutral stimuli was also found in the placebo condition, and was not observed in the THC condition.

Introduction

Significant attention has been given to the effects of drug use and dependence on attentional bias to drug-related stimuli, although other types of stimuli are far less frequently studied and the drug in question has rarely been one that has become increasingly relevant in recent years: marijuana. A growing number of states are allowing the prescribing of marijuana for medical purposes, and several have legalized it for purely recreational usage. Despite this increased acceptance of the drug, there is a noted scarcity of well-designed research surrounding the various effects of marijuana on its users (Gunderson, 2015). The need for studies examining marijuana will only grow more pressing, and an expansion of THC interactions being analyzed studies is necessary to increase understanding of this drug. The purpose of this study was to examine the effect of THC on attentional bias to negative stimuli relative to positive and neutral stimuli in consistent users of marijuana by tracking the eye-gaze of participants as they looked freely between a negative stimulus and either a positive or neutral stimulus.

Neural Effects of THC

With regards to the effects of THC on attention to stimuli, it has been found that THC, like other addictive drugs, causes an increase in dopamine neurotransmission. This increase has the effect of strengthening the attribution of salience to certain environmental cues. Salience is given to stimuli that are most "wanted" by or relevant to the drug user, normally ones associated with drug usage due to it being the cause of activation of this system. With continued drug use, over time the brains of many individuals make semi-permanent adaptations in this neural system that cause them to become highly-sensitized to drug-associated stimuli, which is what leads to increased drug craving and addiction (Robinson & Berridge, 1993). Although this model of the

neural effects of THC on its users does not address how it may be relevant to the perception and salience of any cues but drug-related ones, it may be adapted and used to explain attentional biases to other forms of stimuli. In the proposed study, it could be posited that the more salient of the two picture presentations would be the negative emotional one, due to its suggestion of a potential threat, and that participants in the THC condition will show bias towards it for this reason.

Attentional Bias to Emotional Stimuli and Drug Use

Where attentional bias to emotional stimuli has been studied, it has very rarely been in regards to THC. A unique study which used a pleasantness rating task and an emotional Stroop task to examine cognitive bias for drug-related and emotional stimuli in marijuana users found that participants who had been given THC showed a greater attentional allocation toward drug cues and negatively valenced emotional pictures (Metrick et al., 2015). This would seem to be in agreement with the neural model of craving that was previously discussed, with participants who have been given THC paying greater attention to more salient stimuli. This is the only study that was found to examine the relationship between THC and bias to emotional stimuli, and it is noted by the researchers in this study that tracking participant gaze would be a more effective measure for recording attentional bias than choice tasks (Metrick et al., 2015), supporting the importance of the proposed study in examining this phenomenon.

In studying this seldom researched topic it may prove beneficial to review several of the studies which focused on other substances in relation to attentional bias to emotional stimuli. One study conducted by Lambe, Hudson, and Stewart examined attentional bias to affective stimuli in relation to drinking motives in problem and non-problem drinkers. In this study, the

researchers posited that substance abuse, in this case alcoholism, may be used as a means of either increasing positive emotion or coping with negative emotion, and that whether a person abuses a substance as a coping method or an enhancing method would be associated with an attentional bias to affective stimuli matching their symptoms. It was found that enhancement motivated problem drinkers displayed a bias towards positive stimuli, while coping motivated problem drinkers showed a greater overall distractibility during experimental tasks (Lambe, Hudson, & Stewart, 2015). This result is relevant to the current study because it may be applied to other types of drug use and dependence, namely THC. It may be that participants who use marijuana may be more inclined to be attentionally biased toward stimuli that matches their motivation for using the drug.

With regards to nicotine and attentional bias to emotional stimuli, one study found that administration of a nicotine patch relative to a placebo patch in consistent smokers decreased distraction caused by drug-associated and negative stimuli, suggesting an overall less negative affect in participants with nicotine administration (Gilbert et al., 2006). This finding may suggest that drug use lowers recognition of different types of affect, and may be generalized to the current study to posit that the administration of THC will lower the ability of participants to perceive and allocate attention to varying emotional picture presentations.

Hypotheses

In this study, it was hypothesized that participants in the THC condition, relative to the placebo condition, would display a greater attentional bias to negative emotional stimuli, independent of whether it was paired with a positive or neutral stimuli.

Methods

Legal Issues: Legal Approval and Participant Safety

    Legal approval. The study was approved by all required State and Federal Agencies; specifically, the Illinois Department of Financial and Professional Regulation (IDFPR), Drug Enforcement Administration (DEA), U.S. Food and Drug Administration (FDA), and National Institute on Drug Abuse (NIDA). A Certificate of Confidentiality was also obtained from the National Institutes of Health (NIH) to protect all identifiable research information from forced disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Finally, the study was approved by the SIUC Human Subjects Committee (HSC). The Director of the SIUC Police Department, Todd Sigler, met with Professor David Gilbert and was provided with an overview of the study, given a tour of the laboratory, and provided with information about the Certificate of Confidentiality. Dr. Gilbert also worked out an agreement with Mr. Sigler that campus police at 911 would be contacted by lab personnel if any problems occurred where the participants were a risk to themselves or others, including attempting to leave before passing the sobriety test.

    Participant Safety. There was a small risk that participants could be identified as marijuana users through their association with the study. In order to protect the identities of the participants and keep them from being identified as marijuana users, all participants were addressed by lab personnel only through the use of pseudonyms which were chosen at the beginning of the study. All materials bearing the participants' names and other personal information, including the consent form, were locked away in a secure location such that only the researchers could access them. All participants were notified of these discretionary measures prior to consenting.

Participants

The sample for this study consisted of 16 male Caucasian marijuana users, aged 18 to 28. All participants met the inclusionary criteria and were in compliance with the exclusionary criteria. Of the 16 participants who began the study, 14 completed all experimental sessions and were included in analysis, with 1 participant being removed for failing to complete the second of the two experimental sessions and 1 participant's data being deemed unusable. After initial analysis, it was determined that the data of only 7 participants was fit to include in final statistical analyses, as the data of the other 7 participants was determined to contain too many epochs with excessive confounding artifacts.

Participant Recruitment. Participants were recruited by newspaper ads and postings throughout a Midwestern University and the surrounding community. Detailed phone and in-person screening interviews were used to assess whether individuals met the inclusion criteria for this study. Individuals were not informed during the initial telephone interview of the inclusionary or exclusionary criteria. Participants were instructed not to smoke tobacco or drink alcohol for the 12 hours preceding each of the experimental sessions and not to smoke marijuana for at least 72 hours prior to the session. Only those who both reported having adhered to these abstinence requirements and who had expired breath CO concentrations of less than 10 ppm were included in the data analysis. Participants who indicated a history of drug use during their screening were administered urine samples. To promote drug-abstinence by participants during the course of the study, all individuals were informed that there would be urine drug screenings and that failure to comply with abstinence requirements would be grounds for removal from the study.

Inclusionary criteria. Inclusionary criteria consisted of a history of marijuana use of at least once per month for the past 12 months with current use not exceeding more than three days per week as stipulated by the FDA, having detectable amounts of urine Δ9-THC, and good physical (BMI of 19-26 kg/m2, HR < 104, BP < 140/90) and mental health (as verified by the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I], Biometrics Research Department, New York, NY) (Martens, 2010).

Exclusionary criteria. Exclusionary criteria consisted of a lack of English fluency, less than a high-school education, color-blindness or any other severe visual impairment (uncorrected limited vision, limited movement, lazy eye), women who were actively trying to become pregnant, lactation or pregnancy (testing positive on a urine pregnancy test [Jant Accutest® Rapid Urine Pregnancy Test, Encino, CA]), any current substance use apart from marijuana, alcohol, nicotine, and caffeine, excessive use of any of the listed substances, cognitive impairment resulting from head injury, and any significant neurological, physical, or mental disorder (Martens, 2010). These exclusionary criteria were chosen in order to minimize the presence of extraneous variables which were not measured during the study but could have significantly affected the results.

Equipment and Materials

Picture stimuli. Picture stimuli consisted of color pictures depicting faces displaying different emotions. The picture set consisted of 304 images taken of 12 male and 26 female undergraduate students, ages 18 to 42. Images were taken over a four month period using the Facial Action Coding System devised by Paul Ekman, PhD (Ekman & Friesen, 1977). The Facial Action Coding System is a guide that categorizes facial behaviors based on the muscles

that produce them. The expressions chosen for the picture set consisted of anger, fear, and happiness.

Apparatus. The pictures were presented via a PC with an 18-inch LCD color monitor. Picture presentation was accomplished with a SuperLab™ 2.0 software (Cedrus®, Phoenix, AZ) that sent picture onset information via a serial connection to an Arrington eye-tracking system (Arrington Research, Inc., Scottsdale, AZ) run with a computer. The eye-tracking system consisted of an infrared camera, forehead bar, and chinrest in which the participant's head would be comfortably secured while seated in a padded chair. Gaze direction was measured 30 samples/second continuously during the picture tasks.

Quantified Smoke Delivery System. The Quantified Smoke Delivery System (QSDS), created and patented by Dr. David G. Gilbert, allows for the administration of measured amounts of smoke. While using the QSDS, once per minute participants were instructed to form a complete seal around a tube through which the smoke from a lit cigarette would be delivered. The researcher would then activate the QSDS remotely, which would then deliver the appropriate amount of smoke to the participant for them to inhale. Participants received practice in performing this task until they were proficient and could reliably perform it during experimental sessions.

Humidor. The humidor consists of a plastic box, which is airtight and contains a small bowl containing a 4% saline solution.

Marijuana Cigarettes. Active (containing an estimated 26.25 mg Δ9-THC) and placebo (containing an estimated 0.039 mg Δ9-THC) marijuana cigarettes with a NIDA estimated weight of 907mg and measuring 85mm in length were provided by NIDA for this experiment. The

cigarettes were shipped to the laboratory sealed and frozen, in order to reserve their potency.

Cigarette Storage. Cigarettes were stored immediately upon arrival in a Whirlpool chest freezer locked within a room to which only Dr. Gilbert and the laboratory coordinator had access. In compliance with DEA regulations, records were kept of each cigarette by the researchers.

Experimental Task

Ekman Task. During the Ekman task, participants were placed in the eye-tracking apparatus and informed that they would be presented with a series of pictures pairs. They were instructed to first fixate on a cross in the center of the screen, after which the pictures would appear for 3000ms. During the picture presentations, they were instructed to look freely between the pictures, but never to look at the blank space between them.

Procedure

Participants attended an orientation/practice session (5 hours) and two experimental sessions (3.5 hours each). Each participant sat alone in a small experimental room that was electronically connected to a central control room. The control room contained a server computer for control of experimental tasks, and video display units for monitoring each participant's computer and behavior. Participants earned monetary compensation for completion of the study.

Orientation/practice session. During the orientation session the eligibility of each participant was reviewed, they were given detailed information about the nature of the study, and the consent form was reviewed and signed. After consenting, biological samples were taken, in the form of urine and carbon monoxide content samples. The participants then completed a set of trait questionnaires. After completing the questionnaires, participants were familiarized with and

practiced the tasks that they would be completing during the experimental sessions. Participants also practiced using the QSDS, which would be used during the experimental sessions to administer either the placebo or the THC cigarette.

   Biological samples. During the first week before the first experimental session, participants were required to refrain from smoking marijuana. This period of abstinence continued until the second experimental session was completed. Failure to abstain from smoking marijuana was grounds for removal from the study and forfeiture of compensation. Urine assays were used to demonstrate minimal Δ9-THC metabolite concentrations (ICup 10-panel Urine Drug Test, Instant Technologies, Norfolk, VA). Assessment of participant carbon monoxide (CO) levels consisted of one minute collections in which participants were required to hold their breath for 20 seconds and then to exhale into a CO monitor for a further 20 seconds. Participants were instructed on how to make a complete seal around the cardboard tube that was applied to the CO monitor before each collection and how to slowly and steadily exhale so as to meet the required exhalation time of 20 seconds.

   Physiological monitoring. Blood Pressure (BP; LifeSource One Step Auto Inflate Blood Pressure Monitor, A&D Medical, San Jose, CA) was measured at three points during each of the experimental sessions. The first measurement took place at 15 minutes prior to cigarette administration, the second occurred two minutes after administration, and the final measurement was taken at 60 minutes after administration.

   Experimental Sessions. During the first experimental session, urine and carbon monoxide samples were collected from the participants and they were asked questions about their current status, including what they had eaten that day, how long they had slept, and if they had used

cigarettes, alcohol, drugs, or meds that day. The participants' blood pressure and heart rate were then taken and they were escorted to the experimental room. Participants were administered their cigarette for the session, which would either be a placebo cigarette or would contain THC, using the QSDS, and blood pressure was again taken. After smoking their cigarette, participants were then placed in the eye tracking apparatus and completed the experimental tasks. Once the experimental tasks were completed, participants' blood pressure was again taken and they completed an end of session questionnaire. The second experimental session was conducted in much the same way, save that participants who had been administered a placebo cigarette were this time given a THC cigarette, and vice versa. At the end of the experimental sessions, participants were administered sobriety tasks and then taken to the vehicle of an approved family member or friend who had been recruited to drive them from the experimental sessions to their home. The drivers were required to review and sign a HSC-approved responsibility contract. The drivers were compensated with $5.00 gift cards to Wal-Mart or Kroger that were given during each experimental session from which they picked up the participant. Participants were given $100.00 gift cards as compensation for their completion of both experimental sessions.

Analytic Procedures

Statistical analyses. All ANOVA probabilities involving changes in eye-gaze across time were based on the Huynh-Feldt (1976) correction for sphericity of repeated measures. Non-corrected degrees of freedom are reported for purpose of clarity. Follow-up analyses of simple effects were performed on significant interactions. Analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL).

Eye-gaze processing. In preparation for statistical analyses, the eye-tracking data from each

3000 ms picture presentation epoch produced a sequence of 90 digitized values corresponding to the direction of eye gaze at time increments of 33.3ms (30 samples/s). For each of the dual picture presentations, an in-house Microsoft Excel© program assigned a value of 1.0 to direct gazes at the center of the negative pictures irrespective of visual field of presentation and assigned a value of -1.0 to gazing at the center of the alternative (neutral or positive) picture. All data processing was done blind to the THC condition. Epochs with extensive blink or other artifacts were rejected. Participants with sessions containing numerous epochs with extensive blink or other artifacts were removed from analysis. Epochs containing several or fewer blink artifacts were easily identified by extreme (outside gaze range) values and were automatically corrected using interpolation algorithms. The gaze pattern for each picture was baseline corrected using the median value of the last 20 fixations immediately prior to dual picture onset. In order to make gaze time equal for all participants, 80 points (of the potential 90 total points) were used because individuals take from 198 to 300ms (6 - 10 time points) to move their eyes after the onset of the dual picture. The counting of the 80 time points began with the first point during which eye-gaze was directed away from the central fixation point towards the gaze space of one of the two simultaneously-presented pictures. Thus, for all participants the duration of eye-gaze monitoring was 80 points (2667ms) after initiation of gazing.

Results

Effects of THC on Attentional Bias to Negative Relative to Neutral and to Positive Pictures

As predicted and can be seen in Figure 1, gaze direction across the full 2667ms was moderated by a THC × Valence (neutral vs. positive alternative), $F(1,7) = 6.818$, $p = .035$, partial $\eta^2 = .493$, such that in the placebo condition positive alternative pictures, relative to neutral

alternatives, greatly decreased negative picture attentional bias (viewing time), while in the THC

condition there was no significant difference in attentional bias to negative pictures as a function

of alternative picture valence (positive vs. neutral). In addition, as can be seen in Figure 2, there

was a significant THC x Time interaction (Figure 2), $F(1, 79) = 3.563$, $p = .024$, partial $\eta^2 =$

.337, such that during the first 667ms of gaze time, relative to placebo, THC was associated with

significantly greater (all p's $< .05$) attentional bias towards the negative picture, while

subsequent to this time there were no differences between the two drug conditions, though

during the last 2000ms of viewing THC was consistently associated with reduced negative

attentional bias, though at no point was there a significant difference between the two drug

conditions.

Of the 14 participants who completed the experimental sessions, the data of 7 of them were

removed from analysis due to the presence of numerous epochs containing artifacts that would

have been detrimental to statistical analysis.

Discussion

Drug Type and Emotional Picture Bias

The significant interaction seen between drug type and valence (neutral vs. positive

alternative) could suggest that THC lowered the ability of participants to recognize and

differentiate emotions on human faces, or alternatively lowered the perceived importance of the

recognition and differentiation of presentations of varying emotions. In experimental sessions

where participants completed the Ekman task after having smoked a placebo marijuana cigarette,

they showed a significant bias for pictures depicting a positive emotional face when paired with

a negative emotional picture. When presented with a neutral picture paired with a negative

emotional picture, participants who had smoked the placebo cigarette were biased toward the negative emotional picture. These results suggest that during placebo sessions participants preferred positive pictures to negative ones and negative pictures to neutral ones, as is shown in Figure 1. However, after having smoked a marijuana cigarette containing significant levels of THC, participants showed a much narrower range of bias for any picture, with eye-gaze tending to distribute evenly across all picture types and pairings. These results would seem to imply that the presence of THC had a detrimental effect on the emotional intelligence of the participants, which is defined as the ability of a person to recognize and process both one's own emotions and displays of emotion in others (Cho, Drasgow, and Cao, 2015). THC appeared to inhibit the ability of participants to effectively identify and notice variations in the emotional faces presented in the pictures. This possible link between THC and emotional intelligence has received little attention, and would make an interesting basis for future study.

THC and Initial Orienting Response

The significant interaction seen between drug type and time suggests that an initial orienting response is associated with THC. This sort of orienting response of THC has been noted in previous studies, namely a hyper-attentiveness and motor preparedness to fixate on drug-related stimuli. This response has been observed to be primed and automatic (Field, 2005). It is interesting to note that in this study an orienting response that is commonly associated with drug related cues was found to be associated with presentations of negative affect.

As has been previously discussed, THC provides the user with an increase in dopamine, which has been shown to increase attention to salient stimuli in one's environment. In most studies that examined the effects of THC on attentional bias, the focus was on attention to drug-

associated stimuli in relation to neutral stimuli, where it was consistently found that participants under the influence of THC displayed an automatic and near-instant fixation on the drug-associated stimuli before giving attention to paired neutral stimuli (Field, 2005). This effect was also observed in the current study, albeit with negative emotional stimuli taking the place of drug-associated stimuli. A possible explanation for this result is that the initial orienting response associated with increased levels of dopamine was in this case directed toward the more salient of the two paired emotional stimuli: the one that could be perceived as threatening, in this case displays of anger or fear, and is thus more deserving of assessment.

Limitations

Upon analysis, several effects that were expected to be significant fell just short of this mark. It is the opinion of the researchers that this was due to the small sample size used for this study and the fact that data for some subjects was not able to be used in analysis due to a large number of epochs with extensive blink or other artifacts. If conducted again, the results of this study could be improved and amplified by the recruitment and retention of a larger sample size. This would give the benefit of providing more data and lowering the chance that the data of a significant number of participants would be of poor quality and thus unusable in analysis.

Implications

The implication of a connection between THC usage and lowered attention to emotional variance is one that is not well-discussed, if at all, in the current literature and is deserving of further study. It is also worthy of consideration that the initial orienting response that is associated with raised levels of dopamine due to THC usage is here connected with negative stimuli rather than drug-associated stimuli, as has been studied and documented numerous times.

Due to the unique nature of this study and the near-significant results that were found upon analysis, it would be worthwhile for this study to be repeated with a larger sample size in order to better understand several interactions associated with THC that have so rarely been noted and received attention.

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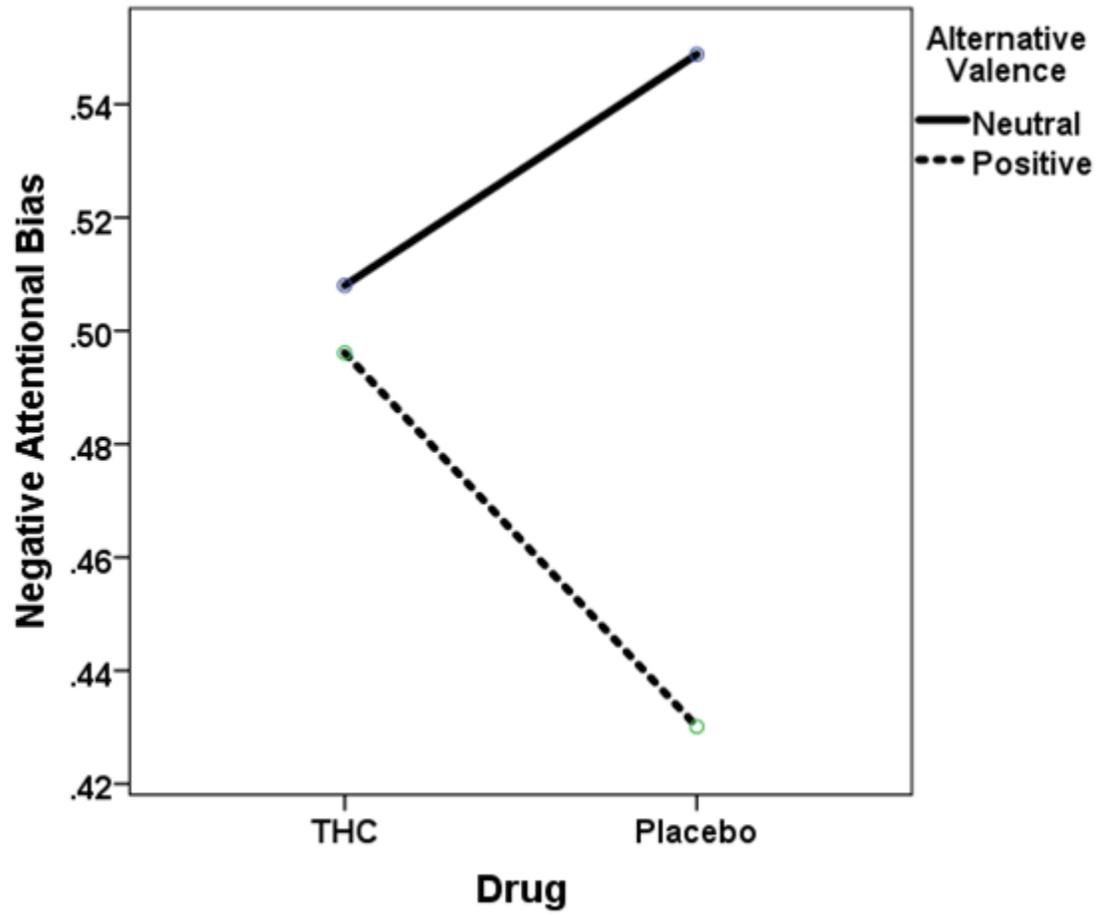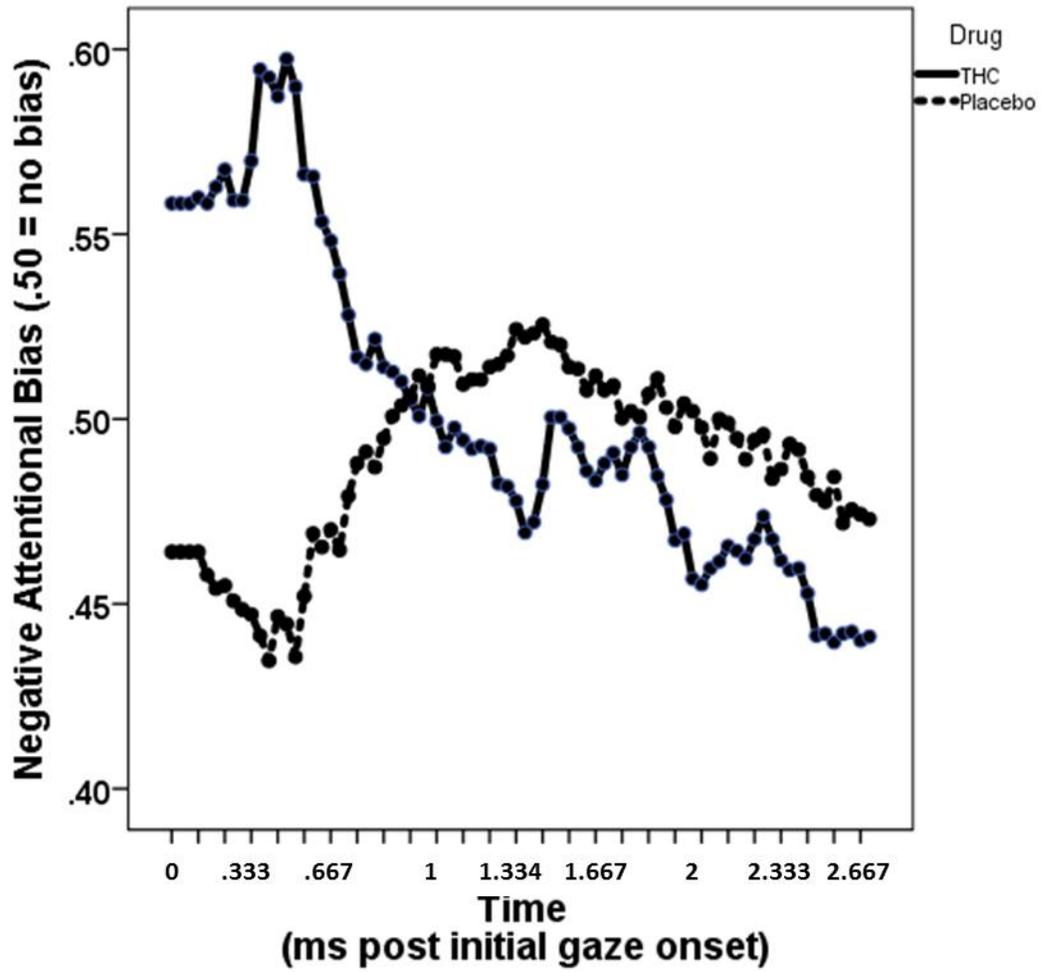
Figures

Figure1. Negative Attentional Bias by THC x Valence

Figure 2. Negative Attentional Bias by THC x Time