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# Circulating Endocannabinoid Concentrations and Sexual Arousal in Women

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## Abstract

**Introduction—**Several lines of evidence point to the potential role of the endocannabinoid system in female sexual functioning. These include results from studies describing the subjective effects of exogenous cannabinoids on sexual functioning in humans and the observable effects of exogenous cannabinoids on sexual functioning in other species, as well as results from studies investigating the location of cannabinoid receptors in the brain and periphery, and the effects of cannabinoid receptor activation on neurotransmitters implicated in sexual functioning. While these lines of research suggest a role for the endocannabinoid system in female sexual functioning, no studies investigating the relationship between concentrations of endogenous cannabinoids (i.e., arachidonoylethanolamide [AEA] and 2-arachidonoylglycerol [2-AG]) and sexual functioning have been conducted in any species.

**Aim—**To measure circulating endocannabinoid concentrations in relation to subjective and physiological indices of sexual arousal in women ($n$ = 21).

**Methods—**Serum endocannabinoid (AEA and 2-AG) concentrations were measured immediately prior to, and immediately following, viewing of neutral (control) and erotic (experimental) film stimuli in a repeated measures design. Physiological sexual arousal was measured via vaginal photoplethysmography. Subjective sexual arousal was measured both continuously and non-continuously. Pearson's correlations were used to investigate the relationships between endocannabinoid concentrations and sexual arousal.

**Main Outcome Measures—**Changes in AEA and 2-AG concentrations from pre- to post-film and in relation to physiological and subjective indices of sexual arousal.

**Results—**Results revealed a significant relationship between endocannabinoid concentrations and female sexual arousal, whereby increases in both physiological and subjective indices of sexual arousal were significantly associated with decreases in AEA, and increases in subjective indices of sexual arousal were significantly associated with decreases in 2-AG.

**Conclusions—**These findings support the hypothesis that the endocannabinoid system is involved in female sexual functioning, with implications for furthering understanding of the biological mechanisms underlying female sexual functioning.

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## Introduction

Despite considerable advances in the last three decades, an understanding of sexual physiology in women is still in its infancy. One area of research which may advance understanding of the physiological mechanisms involved in female sexual function is the investigation of the potential role of the endocannabinoid system in sexual behavior [1, 2]. Findings from several lines of research point to the potential role of this system in female sexual functioning: 1) evidence from the effects of cannabis use on subjective indices of sexual function in humans; 2) evidence from the administration of exogenous cannabinoid agonists and antagonists on observable sexual behaviors in other species; 3) the location of cannabinoid receptors in areas of the brain and peripheral tissues important for sexual functioning; and 4) the effects of cannabinoid receptor activation on neurotransmitters implicated in sexual functioning.

Research results have almost consistently suggested a facilitatory effect of cannabis on subjective indices of sexual function in women [for reviews, see 1, 2]. These include self-reported increases in sexual desire [3-6], orgasmic function [6, 7], and sexual satisfaction, enjoyment, and/or pleasure [4, 6, 7]. However, while these results are suggestive of a possible link between cannabis use and sexual function (and, in fact, with the exception of only one study [8], suggestive of a *positive* association between cannabis use and female sexual function), the data in these studies are based solely on self-report. Numerous other explanations, besides a direct association between the endocannabinoid system and sexual functioning, may also account for the self-reported effects of cannabinoids on sexuality in women. For example, it may be that cannabis enhances sexual experiences by altering either sensation and/or perception [9, 10]. Alternatively, sexual function may be enhanced indirectly through the effects of cannabinoids on anxiety [10, 11], or through cannabis-induced disinhibition which, in turn, may allow for increased relaxation and sensory focus [6, 12].

As a result, while the few studies which have investigated the self-reported effects of cannabis use on sexual functioning in women have, with only one exception [8], shown a facilitatory effect [3-7], the specific effects, the reliability of these effects, and the presence of a direct link between the endocannabinoid system and female sexual functioning have not been established. The results do, however, suggest an area for further research.

With respect to evidence from cannabinoid administration on observable sexual behaviors in other species, several studies provide further support for the hypothesis that the endocannabinoid system may be implicated in the physiology of female sexual behavior [13-18]. However, the results across these studies are in contrast with each other, with some studies finding facilitatory effects of cannabinoid agonists and inhibitory effects of cannabinoid antagonists on sexual behavior [13-15], and other studies finding opposite, inhibitory effects of cannabinoid agonists and facilitatory effects of cannabinoid antagonists on sexual behavior [16-18]. Given these contradictory findings, the role of the endocannabinoid system in sexual behavior in non-human species remains unclear and further research aimed at reconciling these findings is needed. More generally, it must be recognized that animal models do not always translate to humans [19]. Therefore, without research employing physiological measures and direct examination of the role of the endocannabinoid system in human female sexual physiology, no definitive conclusions regarding the role of the endocannabinoid system in human female sexual behavior can be made.

The third line of evidence that is suggestive of a role of the endocannabinoid system in female sexual functioning comes from the location of cannabinoid receptors in areas of the

brain and peripheral tissues important for sexual functioning. Endocannabinoid receptors are highly abundant in the brain, being located in structures such as the hypothalamus, hippocampus, cerebellum, amygdala, striatum, and throughout the cortex and basal ganglia [20-23]. As discussed by Gorzalka and colleagues [2], the distribution of cannabinoid receptors throughout these brain structures positions this system to modulate sexual behavior through a number of possible mechanisms. In addition to high densities in the brain, cannabinoid receptors are also present in peripheral tissues implicated in sexual function, including the adrenal glands (which are a source of androgens) and reproductive tissues such as the ovaries [24] (which are a major source of both estrogens and androgens).

The final line of evidence in support of a potential role for the endocannabinoid system in female sexual behavior comes from the known effects of cannabinoid receptor activation on neurotransmitter release. The cannabinoid $CB_1$ receptor is a presynaptic receptor in the central nervous system whose activation results in the inhibition of neurotransmitter release. As $CB_1$ receptors are located on axon terminals that release dopamine, serotonin, GABA, glutamate, and acetylcholine [25-27], it is these neurotransmitters that are affected and regulated by $CB_1$ receptor activation. Several of these neurotransmitters play key roles in sexual functioning and behavior, particularly serotonin and dopamine [e.g., 28, 29].

Together, these four lines of evidence suggest that the endocannabinoid system may play a role in female sexual behavior. However, because no studies employing physiological measures to examine the role of exogenous cannabinoids on sexual function in women, or of the effects of changes in sexual function *on endocannabinoid concentrations* in women, have been conducted, the role of the endocannabinoid system in human female sexual functioning remains unknown.

## Aim

The aim of the current research was to investigate the relationship between the endocannabinoid system and sexual function in women. Specifically, the objective of this study was to investigate whether changes in physiological and subjective sexual arousal are accompanied by changes in serum endocannabinoid (i.e., arachidonoylethanolamide [anandamide or AEA] and 2-arachidonoylglycerol [2-AG]) concentrations, and, if found to be the case, to assess the direction of these changes (i.e., whether endocannabinoid concentrations increase or decrease in relation to increased sexual arousal). Sexual arousal, as opposed to other indices of sexual function/response (such as desire and orgasm), was examined in this research given the availability of validated measures for both physiological and subjective sexual arousal.

Based, in part, on the reported subjective effects of cannabis consumption on sexual function in humans, it was hypothesized that there would be a correlation between endocannabinoid concentrations and changes in sexual arousal. Further, it was hypothesized that this relationship would be positive, with increased sexual arousal being associated with increased endocannabinoid (AEA and 2-AG) concentrations. This latter hypothesis was based on the fact that past studies in women have, with only one exception [8], found cannabis to be related to enhanced perceptions of sexual function [3-7], suggesting that elevated cannabinoid concentrations are associated with heightened sexual response.

This is the first study to date to examine serum endocannabinoid concentrations in relation to sexual function and, more specifically, in relation to sexual arousal, in women.

# Methods

## Participants

Participants were 21 medically healthy premenopausal women between the ages of 19–45. "Medically healthy" was defined as being in good physical health with no history of chronic medical illnesses (including hormonal disorders such as diabetes) and no indications of current acute infections, as determined by self-report. In addition, no participants were currently taking, or had previously taken in the last six months, any prescribed medications other than oral contraceptives. Participants were also screened for the presence of any mental health concerns or the presence of any sexual difficulties. Further exclusion criteria included the use of any illicit substances (including cannabis) in the last month, current or past pregnancy over the last year, current breastfeeding of a child, and natural or surgical menopause. Finally, exclusively homosexual women were also excluded, as the film stimuli employed to elicit sexual arousal were directed at heterosexual women. Participant characteristics are presented in Table 1.

## Apparatus and Materials

**Film Stimuli—**Film stimuli consisted of two, 14-min. films which included a 1-min. display of the word "relax" followed by a 3-min. video clip containing neutral material (either a clip from a documentary about shallow seas or a clip from a documentary about birds), followed by a 10-min. video clip containing either erotic material (experimental session) or a neutral documentary about caves (control session). The erotic material involved a nude, heterosexual couple engaging in foreplay and subsequent sexual intercourse and has previously been found to increase physiological and subjective sexual arousal reliably in women [30, 31]. The different segments of the films were professionally spliced together to form one continuous videotape with audio accompaniment.

**Vaginal Photoplethysmograph—**Vaginal photoplethysmography [32] was used to measure physiological sexual arousal. Vaginal Pulse Amplitude (VPA), rather than Vaginal Blood Volume (VBV), was used as the outcome measure in this research as VPA has been shown to be a more sensitive measure of sexual arousal [33-35]. VPA reflects phasic changes in vaginal engorgement with each heart beat, such that higher amplitudes indicate greater genital engorgement [33]. The vaginal photoplethysmograph is the most validated and most commonly used physiological instrument to measure sexual arousal in women [36].

The photoplethysmograph was turned on 30 min. prior to use in order to minimize potential light history and temperature sensitivity effects. After the photoplethysmograph had been inserted, a 5-min. adaptation period occurred prior to onset of the experimental stimuli. Psychophysiological data were continuously recorded during presentation of the film clips using Acqknowledge III, Version 3.5 (BIOPAC Systems Inc., Santa Barbara, CA), a Model MP100WSW data acquisition unit (BIOPAC Systems Inc.), and an HP Vectra Celeron personal computer. As in previous research [31, 37, 38], data were analyzed in 30-s. segments and then averaged separately over the neutral and erotic film segments in order to derive two data points per participant per session: one for the initial neutral segment, and one for the subsequent neutral (control session) or erotic (experimental session) segment.

**Non-Continuous Subjective Measurement of Arousal—**Before and after each of the film sequences, a subjective measure of arousal was collected via a one-page, self-report Film Scale containing 34 items. The Film Scale is adapted from Heiman and Rowland [39] and assesses six domains: overall subjective sexual arousal (1 item), mental sexual arousal (6 items), perceptions of physiological sexual arousal (5 items), autonomic arousal (5 items),

anxiety (1 item), positive affect (5 items), and negative affect (11 items). Items are rated on a 7-point Likert scale from *not at all* (1) to *intensely* (7). The scale has been found to be a valid and sensitive measure of emotional reactions to erotic stimuli [39-41].

**Continuous Subjective Measurement of Sexual Arousal—**A device, previously termed an "arousometer" [42, 43], was constructed and employed in this study to measure continuous subjective sexual arousal. This device consists of a computer mouse mounted on a metal track with 10 equally spaced intervals ranging from -2 ("sexually turned off") to 7 ("highly sexually aroused"), with 0 reflecting neutral, or the absence of positive or negative sexual feelings. Participants are instructed to continuously monitor and indicate subjective feelings of sexual arousal during viewing of film stimuli through manipulation of the computer mouse along the numbered track. Resistance built into the device at each number allows participants to feel when they are moving up or down an interval without having to take their gaze off of the film stimuli. The computer mouse provides input to a software program written to detect the position of the pointer every 0.5 seconds.

**Testing Conditions Interview—**In order to control for factors that can affect endocannabinoid concentrations, an interview relating to physical state immediately prior to participation in each session was developed and conducted. This interview involved questions verifying that participants had fasted prior to each session (as caloric intake is associated with changes in endocannabinoid concentrations) and that no illicit substances had been used in the past month. In addition, the interview queried about current phase of the menstrual cycle and about current, self-reported stress levels.

**Derogatis Sexual Functioning Inventory—**The Derogatis Sexual Functioning Inventory (DSFI) [44, 45] was administered to participants in order to verify the initial screening that all participants were in the normative range for sexual functioning and that they did not suffer from any significant psychopathology. The DSFI is comprised of ten distinct subtests including one diagnostic subtest, the Brief Symptom Inventory (BSI), which is an independent measure of psychological symptoms. A total Sexual Functioning Index (SFI) score is derived by standardizing and then summing the ten subscale scores. This index reflects the overall quality of current sexual functioning. In addition, a single-item Global Sexual Satisfaction Index (GSSI) provides information on the respondent's self-reported quality of sexual relationship functioning. With respect to discriminant validity, the DSFI has been shown to be a valid measure for differentiating sexually functional and dysfunctional women [45, 46].

**Female Sexual Function Index—**The Female Sexual Function Index (FSFI) [47] was also administered to participants, to verify again that all participants fell within the normative range for sexual functioning. The FSFI is a 19-item measure assessing desire, sexual arousal, lubrication, orgasm, satisfaction, and pain during sexual activity over the past month. This measure was included because it collects more detailed information about specific areas of potential sexual difficulty than the DSFI. As with the DSFI, the FSFI has been shown to be a valid measure for differentiating sexually functional and dysfunctional women [47].

**Beck Depression Inventory-II & Beck Anxiety Inventory—**As both depression and anxiety are known to affect sexual functioning [e.g., 48], and depression is also associated with reduced circulating endocannabinoid concentrations [49-51], the Beck Depression Inventory-II (BDI-II) [52] and the Beck Anxiety Inventory (BAI) [53], were administered to participants in this study to assess for depression and anxiety symptomatology, respectively. The BDI-II is a 21-item self-report measure assessing various symptoms of depression

including cognitive, physical, and affective symptoms. The BAI is a 21-item self-report measure assessing both physical and cognitive symptoms of anxiety. Both the BDI-II and BAI have good psychometric properties [e.g., 52, 53] and have been used extensively in both clinical and research settings.

**Antecubital Venipuncture—**Antecubital venipuncture to obtain serum for the measurement of endocannabinoid concentrations involved taking a total of four, 8-ml blood samples (two per session) using 21-gauge, ¾-inch butterfly needles attached to Vacutainer serum separating tubes. Fresh needles were used for each blood draw and blood was drawn from either the left or the right antecubital fossa depending on the preference of the participant and the ease with which veins could be located.

**Serum Separation, Storage, and Analysis—**Blood samples were left in the serum separating tubes at room temperature for 30 min. following venipuncture. Samples were subsequently centrifuged for 15 min. at 1000 × g, then aspirated, divided into aliquots, and frozen at -80°C until all data for the study had been collected.

At study completion, all serum samples (1 ml each) were thawed and made to a 15% ethanol solution plus the internal standards [$^2H_8$]-AEA (16.9 pmol) and [$^2H_8$]-2-AG (46.5 pmol) (Cayman Chemicals, Ann Arbor, MI). Samples were vortexed and centrifuged at 1000 × g for four min. The supernatant was loaded on C18 columns conditioned with 1 ml redistilled ethanol and 3 ml of distilled water added sequentially. The remaining pellet was washed with 100 μL of 15% ethanol and recentrifuged for 3 min. Resulting supernatant was loaded onto the C18 columns, which were washed with 5 ml double distilled water and eluted with 1 ml ethyl acetate. The ethyl acetate layer in the resulting elute was removed and dried under $N_2$. Residual lipids in the water phase were extracted by mixing with an additional 1 ml of ethyl acetate; after separation of the layers, this was added to the original ethyl acetate layer. Once dried, samples were re-suspended in 20 μL of methanol and frozen at -80°C. AEA and 2-AG were quantified using isotope-dilution, atmospheric pressure, chemical ionization and chromatography/mass spectrometry (LC-APCI-MS). This procedure is described in detail [54], and is identical to that used in previous research involving the measurement of AEA and 2-AG in human serum [51, 55].

## Procedure

Participants were recruited via advertisements posted throughout and surrounding the campus of a large western Canadian university. Advertisements sought out “medically healthy adult women for a study on the physiology of female sexual arousal.” The advertisements also included information on eligibility and exclusion criteria and indicated that an honorarium in exchange for study participation would be provided. Women interested in participating were asked to call the research laboratory for further information.

Upon calling the laboratory, women were told about the study in detail and were given the opportunity to ask questions. Women were also given as much time as they required to make a decision about their participation. Women who expressed interest in taking part in the study were then asked a number of questions in order to ensure that they met all inclusion and exclusion criteria for the study. Those who did were then scheduled for the first of two sessions held on consecutive days to try to ensure that both sessions took place during the same phase of the menstrual cycle. Participants were asked to fast on the morning of their sessions and to refrain from alcohol use in the previous 24 hr. All participants had both sessions scheduled at the same time of the morning to avoid confounding of endocannabinoid concentrations with diurnal hormone variations, and the sessions were counterbalanced across participants.

At the beginning of the first session, participants were shown the laboratory and the equipment used to measure sexual arousal and collect blood. The study purpose was re-explained, participants were given the opportunity to ask questions, and written informed consent was obtained. Participants then took part in the brief testing conditions interview and were asked to complete the questionnaire package containing the DSFI, FSFI, BDI-II, and BAI.

Participants were then instructed on how to insert the vaginal photoplethysmograph with the aid of diagrammed instructions. After instructions were provided, the female researcher left the participant room (an internally-locked room adjacent to the experimenter's room) to allow the participant to insert the vaginal photoplethysmograph in private. Participants remained clothed and were able to cover themselves with a blanket at all times.

Once the photoplethysmograph was comfortably inserted, the experimenter asked the participant for permission to re-enter the room in order to perform the first venipuncture. Participants were seated comfortably in a reclining chair and venipuncture involved taking 8 ml of blood from the antecubital fossa of the left or right arm.

Immediately after the first venipuncture, participants were instructed to complete the 1-page subjective measure of arousal Film Scale asking about their current subjective ratings of sexual arousal, autonomic arousal, anxiety, and positive and negative affect. Participants then took part in a laboratory-induced hyperventilation (LIH) protocol in order to enhance physiological sexual arousal to more closely approximate levels found in naturalistic settings. LIH is a procedure which has been found to reliably increase sympathetic nervous system (SNS) activity and, thus, physiological sexual arousal [31, 38]. Previous research has shown that sexual arousal enhanced by increased SNS activity can reveal the effects of a pharmacological intervention (clonidine) on sexual arousal that is not otherwise apparent when sexual arousal is not elevated via increased SNS activity [56]. Similarly, sexual arousal enhanced via increased SNS activity has been found to discriminate women with various sexual difficulties [57]—findings which are again not apparent in the absence of increased SNS activity.

The LIH procedure involved two min. of rapid, deep breathing at a rate of 30 breaths/min. Participants were asked to breathe along to a pre-recorded audiocassette of paced respiration and asked to breathe in and out as deeply as possible. The experimenter remained in the room with the participant during the LIH procedure to ensure similar breathing patterns across participants.

As soon as participants completed the LIH protocol, the experimenter left the room and participants were shown the first of two films (one film per session), presented in a randomized, counterbalanced fashion on a colour television positioned where participants could sit comfortably with a full view of the screen. During presentation of the films, physiological sexual arousal was measured via the vaginal photoplethysmograph and participants were asked to continuously monitor and indicate their subjective feelings of sexual arousal with the use of the "arousometer."

Immediately following the end of the film presentation, the experimenter again asked for permission to enter the participant room in order to conduct the post-film venipuncture. After the venipuncture procedure was completed, the experimenter left the room and the participant was once again asked to complete the subjective measure of arousal Film Scale; however, this time, participants were asked to report on any subjective sexual arousal, autonomic arousal, anxiety, and positive and negative affect experienced *during* the film they had just watched. Thereafter, participants were instructed to remove the

plethysmograph and to proceed next door to the experimenter room in order to ask any questions in anticipation of the second session.

The second session was identical to the first session except that participants were shown a different film (i.e., either the film containing all neutral material or the film containing erotic material, depending on which film they had already previously seen). In addition, following the end of the second session, all participants were debriefed. As part of their debriefing, participants were given a printout of their physiological sexual arousal profiles as measured by the photoplethysmograph and these profiles were explained to them. Finally, participants were also given a $50.00 honorarium. The research protocol was approved by the Clinical Research Ethics Board at the university where the study was conducted.

## Statistical Analyses

Paired samples t-tests were used to investigate the effects of the video stimuli on physiological sexual arousal in the control versus the experimental conditions. Multivariate analyses of variance for repeated measures were used to investigate the effects of the video stimuli on the three indices of subjective sexual arousal (subjective physiological sexual arousal, mental sexual arousal, and overall subjective sexual arousal). Pearson product moment correlation coefficients were used to investigate the correlations between endocannabinoid (AEA and 2-AG) concentrations and physiological and subjective indices of sexual arousal. Correlations for physiological sexual arousal were assessed by correlating percent increase scores in VPA over the course of the film stimuli with difference scores in AEA and 2-AG concentrations from pre-film to post-film in each condition. Percent increase scores, rather than difference scores, were calculated for VPA, given that the plethysmograph has no discernable zero-point. VPA percent increase scores were calculated by subtracting the mean VPA response during the neutral baseline film from the mean VPA response during the subsequent neutral (control) or erotic (experimental) films, dividing by the mean VPA response from the neutral baseline film, and then multiplying by 100.

Correlations for the subjective measure of arousal were assessed by correlating difference scores in ratings of subjective sexual arousal with difference scores in AEA and 2-AG concentrations from pre-film to post-film in each condition. Difference scores for subjective measures were computed by subtracting pre-film values from post-film values for each sub-scale.

In all cases, a $p$ level of less than 0.05 was deemed statistically significant.

## Results

### Participant Sexual and Affective Characteristics

In support of the screening used to exclude women with current sexual difficulties, all participants scored within one standard deviation of the mean of sexually functional women on both the FSFI and the DSFI. In support of the screening used to exclude women with significant mental health symptoms, participants scored in the minimal range for depression on the BDI-II ($M$ = 6.67; $SD$ = 5.87), in the mild range for anxiety on the BAI ($M$ = 10.81; $SD$ = 10.86), and within one standard deviation of the mean for healthy controls with respect to psychological symptoms on the BSI [$M$ ($T$-score) = 47.52; $SD$ = 9.37].

### Effects of Film Stimuli on Physiological and Subjective Sexual Arousal

A significant difference was found between physiological sexual arousal in the experimental (erotic) condition versus the control (neutral) condition, with physiological sexual arousal significantly greater in the former than in the latter [$t(20) = 2.26$, $p = .035$; see Figure 1].

With respect to the three non-continuous indices of subjective sexual arousal (i.e., subjective physiological sexual arousal, mental sexual arousal, and overall subjective sexual arousal), a multivariate analysis of variance for repeated measures revealed an overall difference in subjective sexual arousal between the experimental and control conditions [$F(3,18) = 24.16$, $p < .001$]. Follow-up univariate tests revealed significant differences for non-continuous subjective physiological sexual arousal [$t(20) = 7.32$, $p < .001$], mental sexual arousal [$t(20) = 7.76$, $p < .001$], and overall subjective sexual arousal [$t(20) = 6.63$, $p < .001$], with the experimental condition again leading to increased indices of non-continuous sexual arousal compared to the control condition (see Figure 2).

Finally, a significant difference between the experimental and control conditions was also found for continuous subjective sexual arousal as measured by the "arousometer" [$t(19) = 8.40$, $p < .001$], with the experimental condition leading to increased subjective sexual arousal as compared to the control condition (see Figure 3).

## Endocannabinoid Concentrations

Pre- and post-film endocannabinoid (AEA and 2-AG) concentrations (means and standard deviations) in the experimental and in the control conditions are presented in Table 2. No significant differences between baseline endocannabinoid concentrations in the experimental versus the control condition were found for either AEA or 2-AG (all *p*s > .10).

## Effects of Film Stimuli on Endocannabinoid Concentrations

Changes in endocannabinoid (AEA and 2-AG) concentrations from pre-film to post-film in the experimental and control conditions are presented in Figures 4 and 5, respectively. A significant decrease in AEA concentrations was observed from pre-film to post-film in the experimental condition [$t(20) = 2.54$, $p = .020$]. In contrast, no significant change in 2-AG concentrations was observed from pre-film to post-film in the experimental condition [$t(20) = 0.50$, $p > .05$], and no significant changes in either AEA or 2-AG concentrations were observed from pre-film to post-film in the control condition [AEA: $t(20) = 0.43$, $p > .05$; 2-AG: $t(20) = 1.65$, $p > .05$].

## Relationship Between Endocannabinoids and Sexual Arousal

Pearson product moment correlations between endocannabinoid concentrations, physiological sexual arousal, and subjective indices of sexual arousal are presented in Table 3, along with descriptive statistics (means and standard deviations) in terms of changes from pre-film to post-film for these variables. A significant positive correlation was found between AEA and 2-AG change scores in the experimental condition ($r = .49$, $p = .023$). This correlation approached significance in the control condition ($r = .43$, $p = .053$).

With respect to the relationship between changes in endocannabinoid concentrations and changes in sexual arousal, as can be seen in Table 3, changes in AEA concentrations from pre-film to post-film in the experimental condition were significantly but negatively correlated with changes in physiological sexual arousal ($r = -.48$, $p = .026$), such that as physiological sexual arousal increased over the course of the erotic film, serum AEA concentrations decreased. Similarly, significant negative correlations were found in the experimental condition between changes in AEA concentrations and both continuous subjective sexual arousal ($r = -.60$, $p = .005$), and non-continuous mental sexual arousal ($r = -.51$, $p = .018$). A negative correlation approaching significance was found between changes in AEA concentrations and changes in non-continuous overall subjective sexual arousal ($r = -.43$, $p = .052$). No significant correlation was found between changes in AEA concentrations and non-continuous subjective physiological sexual arousal ($p > .09$).

As can be seen in Table 3, with respect to changes in 2-AG concentrations from pre-film to post-film in the experimental condition, changes in 2-AG were significantly negatively correlated with continuous subjective sexual arousal ($r$ = -.63, $p$ = .003), and both non-continuous subjective physiological sexual arousal ($r$ = -.54, $p$ = .011) and non-continuous overall subjective sexual arousal ($r$ = -.66, $p$ = .001). No significant correlations were found between changes in 2-AG concentrations and either physiological sexual arousal ($p$ > .45), or non-continuous mental sexual arousal ($p$ > .10).

In the control condition, no significant correlations were found between changes in AEA concentrations from pre-film to post-film and any measures of sexual arousal, whether physiological or subjective. Changes in 2-AG concentrations from pre-film to post-film in the control condition were marginally significantly correlated with changes in physiological sexual arousal ($r$ = -.43, $p$ = .051). No significant correlations were found between changes in 2-AG concentrations and any of the subjective indices of sexual arousal in the control condition (see Table 3; all $p$'s > .07).

With respect to a relationship between baseline endocannabinoid concentrations and subsequent sexual arousal, significant relationships between baseline AEA concentrations and changes in both physiological sexual arousal ($r$ = .50, $p$ = .021) and continuously measured subjective sexual arousal ($r$ = .56, $p$ = .010) were found in the experimental condition. Further, there was a significant relationship between baseline 2-AG concentrations and continuously measured subjective sexual arousal in the experimental condition ($r$ = .49, $p$ = .027). No other significant relationships between baseline endocannabinoid concentrations and indices of sexual arousal were found, either in the experimental or the control condition (all $p$'s > .05).

### Relationship Between Endocannabinoids and Affect, Stress, Days Since Start of Last Menstruation, and Subjective Autonomic Arousal

In the experimental condition, changes in 2-AG concentrations from pre-film to post-film were significantly negatively correlated with changes in perceived autonomic arousal over the course of the film stimuli, such that as perceived autonomic arousal increased over the course of the film, 2-AG concentrations significantly decreased ($r$ = -.44, $p$ = .046). This relationship was not significant in the control condition ($p$ > .05).

No significant associations were found between endocannabinoids and affect (depression, anxiety, positive affect, negative affect), self-reported stress concentrations, or days since the start of the most recent menstrual cycle (all $p$'s > .05).

### Relationships Between Sexual Arousal and Affect, Stress, Days Since Start of Last Menstruation, and Subjective Autonomic Arousal

In the experimental condition, significant correlations were found between (1) positive affect and: non-continuous mental sexual arousal ($r$ = .62, $p$ = .003), non-continuous subjective physiological sexual arousal ($r$ = .67, $p$ = .001), and non-continuous overall subjective sexual arousal ($r$ = .65, $p$ = .001), such that increases in non-continuous subjective sexual arousal over the course of the film were accompanied by increases in positive affect; and (2) subjective autonomic arousal and: both non-continuous subjective physiological sexual arousal ($r$ = .62, $p$ = .002) and non-continuous overall subjective sexual arousal ($r$ = .52, $p$ = .016), such that increases in these indices of subjective sexual arousal were accompanied by increases in subjective autonomic arousal.

No significant correlations were found between physiological or continuous indices of sexual arousal and either positive affect or subjective autonomic arousal. Similarly, no

significant correlations were found between any of the indices of sexual arousal and stress, days since start of the most recent menstrual cycle, depression, anxiety, or negative affect (all *p*'s > .05) in the experimental condition. In the control condition, no significant correlations between any of these factors and sexual arousal were found (all *p*'s > .05).

## Conclusions

The results of this experiment revealed significant associations between endocannabinoid concentrations and female sexual arousal. In fact, this study provides the first evidence to date of alterations in circulating endocannabinoid concentrations in direct relation to changes in not only *physiological*, but also *subjective* sexual arousal in women. AEA concentrations dropped significantly as physiological sexual arousal measured by the vaginal photoplethysmograph, continuous subjective sexual arousal measured by the "arousometer," and mental sexual arousal measured by the Film Scales, increased while participants watched the erotic film. AEA also decreased in conjunction with overall subjective sexual arousal measured by the Film Scales, although this relationship was only marginally significant. 2-AG concentrations were significantly negatively correlated with increased perceptions of physiological sexual arousal, overall subjective sexual arousal, and increased continuous subjective sexual arousal. In other words, the findings were consistent between physiological and subjective measures that a decrease in circulating concentrations of endocannabinoids was associated with increased sexual arousal. Supporting the conclusion that the drop in endocannabinoid concentrations was related specifically to increased sexual arousal, no significant changes in endocannabinoid concentrations were seen in the control condition.

The fact that relationships between circulating endocannabinoid concentrations and sexual arousal were found in this study supports the over-arching hypothesis that the endocannabinoid system is associated with female sexual function. SNS activity naturally increases as sexual arousal increases [58], and as both SNS activity and endocannabinoids have a functional and structural link to adrenergic and noradrenergic activity [59], it is possible that the relationship between the endocannabinoid system and sexual arousal is mediated by noradrenergic and/or adrenergic activation. The nature of the association found in this study was, however, contrary to the original study hypotheses. It was originally hypothesized that endocannabinoid concentrations would *increase*, rather than decrease, in relation to increased sexual arousal. This hypothesis was based, in part, on findings of past studies in which women generally reported enhanced sexual functioning while under the influence of cannabis [3-7], although no data on the direct effects of cannabis on objective sexual psychophysiology exist.

Recent animal studies employing the CB1 receptor agonists HU-210 and CP55,940, and the antagonist AM251, support the idea that cannabinoids may, in fact, be related to *decreased* sexual functioning [16-18]. Further, our results of a negative correlation between sexual functioning and endocannabinoids, while seemingly incongruent with past results that revealed self-reported beneficial effects of cannabis on sexual function in women, are not incongruent with literature of the effects of other psychotropic substances on sexual function. The latter literature has shown that while individuals may report enhanced sexual functioning while under the influence of certain substances, these substances are often, in reality, associated with decreased physiological sexual functioning [e.g., 60]. As previously discussed, there are multiple reasons that individuals may perceive cannabis as sexually enhancing.

The fact that this experiment did not find a significant decrease in 2-AG over the course of the erotic film, and that this study did not find significant correlations between 2-AG and

physiological sexual arousal, between 2-AG and mental sexual arousal, and between AEA and perceptions of physiological sexual arousal, may be indicative of several possibilities. It is possible that the lack of significant associations between these variables were the result of the fact that this experiment was a small experiment with only 21 participants. As such, it is possible that significant findings with respect to these relationships would be found in studies employing a larger sample.

Alternatively, it is possible that the two endocannabinoids have differential associations with different indices of sexual arousal. AEA and 2-AG have been found to respond differentially to stress and other non-sexual stimuli in both humans [e.g., 61] and non-human species [e.g., 62]. As a result, it is also possible that differential associations extend to sexual arousal. This seems most plausible with respect to the relationship between the two endocannabinoids and physiological versus subjective sexual arousal. Basson and others have challenged the concept of physiological and subjective sexual arousal as inseparable events, and have instead proposed a classification of female sexual arousal disorder that distinguishes physiological from subjective sexual arousal [63-66]. The current study may, in fact, provide further evidence for this differentiation by revealing that the endocannabinoid system is differentially associated with physiological and subjective sexual arousal; however, this remains purely speculative.

This study did not find any significant relationships between endocannabinoids and factors which have previously been associated with endocannabinoid concentrations such as stress, depression, and anxiety [49, 51, 67]. This was not surprising as this study excluded women with significant psychological symptoms. Thus, little variability between participants existed on these variables, minimizing the chances that any significant correlations between these factors would be found. In contrast, past studies which found relationships between endocannabinoid concentrations and affective states were conducted by comparing endocannabinoid concentrations in women diagnosed with clinical depression versus healthy controls. The present research did find that 2-AG was significantly negatively correlated with self-perceived autonomic arousal in the experimental condition, but as self-perceived autonomic arousal was also significantly correlated with perceived physiological sexual arousal and overall subjective sexual arousal (a logical finding given that sexual arousal is associated with increased SNS activity), this correlation is to be expected.

This experiment belongs to only a handful of studies to date which have examined the relationship between circulating endocannabinoids and behavioral measures. As is the case with all research, however, this study had some specific limitations which may have influenced the results, as well as the conclusions that could be drawn. These limitations will hopefully be addressed in future studies. As already mentioned, one limitation was that data were based on a relatively small sample size. The size of the sample used in the current research is quite typical for sexual psychophysiology studies with women; however, the limited size of the sample, nonetheless, increases the risk of Type II errors and it is possible that other significant associations between endocannabinoid concentrations and sexual arousal were missed. A second limitation is that this study used discrete sampling methods to measure endocannabinoid concentrations. Sampling serum continuously, rather than discretely, would allow for a greater assessment of the exact relationship between sexual arousal and the endocannabinoid system. For example, it cannot be ruled out that endocannabinoid concentrations increased (rather than decreased) during the period of sexual arousal, and that rebound decreases in endocannabinoid concentrations were detected in the post-film serum measurements. This possibility is not deemed likely, given that post-film serum samples were obtained immediately following the cessation of the film stimuli, and given that it is unlikely that sexual arousal levels returned to baseline in such a brief period of time; however, without continuous sampling methods, this possibility cannot be

dismissed. Finally, this research measured endocannabinoid concentrations in serum, as opposed to measuring endocannabinoid concentrations in cerebrospinal fluid. Although serum concentrations may reflect brain concentrations (given that endocannabinoids cross the blood-brain barrier), direct measurement of endocannabinoid concentrations in cerebrospinal fluid would provide additional information about the role of the endocannabinoid system in female sexual arousal.

Nevertheless, the results of this study have numerous important implications and highlight further areas for study. First, although much more research is needed in order to understand the exact nature of the relationship between female sexual arousal and the endocannabinoid system, the results of this study have exciting implications for furthering understanding of female sexual physiology and female sexual dysfunctions. For example, this study found that sexual arousal was related to decreased endocannabinoid concentrations. An interesting area for further research would be the investigation of whether women with female sexual arousal disorder (FSAD) suffer from dysregulation of the endocannabinoid system. For example, perhaps women with FSAD have a more active endocannabinoid system and/or baseline endocannabinoid concentrations that are too high for optimal sexual function. If this were found to be the case, pharmacological agents that inhibit the production and release of endocannabinoids, or that increase breakdown of these chemicals, may prove beneficial as a treatment. Further, possible sexual side effects (both positive and negative) from pharmacological agents that act on the endocannabinoid system and that are currently being developed for various non-sexual disorders could be anticipated.

Second, the results of this study suggest that cannabinoid receptor agonists, such as cannabis, may impair sexual arousal in women. Given that cannabis has a reputation as being an aphrodisiac, and that some research has found that individuals specifically use cannabis to try to facilitate sexual function, the use of cannabis for this purpose may be counter-productive. Future research examining the direct, acute effects of both cannabinoid receptor agonists and antagonists on subjective and physiological sexual arousal in women would be even more conclusive of a role of the endocannabinoid system on female sexual function; however, the ethical constraints on administering cannabinoid agonists to humans in the laboratory make this research difficult to conduct.

Finally, future research should aim to expand the focus of this research from female sexual arousal to other indices of sexual function such as sexual desire and orgasm. This seems particularly warranted given that past studies on the self-reported effects of cannabis consumption on female sexuality have most often pertained to these two indices, as opposed to the effects of cannabis on sexual arousal. Sexual arousal, rather than sexual desire and/or orgasm, was chosen as the focus of the current research given the availability of a validated, physiological measure of sexual arousal (i.e., vaginal photoplethysmography); however, if/when validated, physiological measures of sexual desire and orgasm become available, research on these sexual outcomes will be important and informative.

Overall, this study provides novel and exciting results that have significant implications for both theory and practice in relation to female sexual function and the treatment of female sexual difficulties. Research that not only replicates these findings, but that also expands on these findings by examining the effects of cannabinoid agonists and antagonists on both subjective and physiological sexual arousal in women with and without sexual difficulties, and that examines the role of the endocannabinoid system in other phases of sexual response, such as desire and orgasm, will further elucidate the role of this system in female sexual function.

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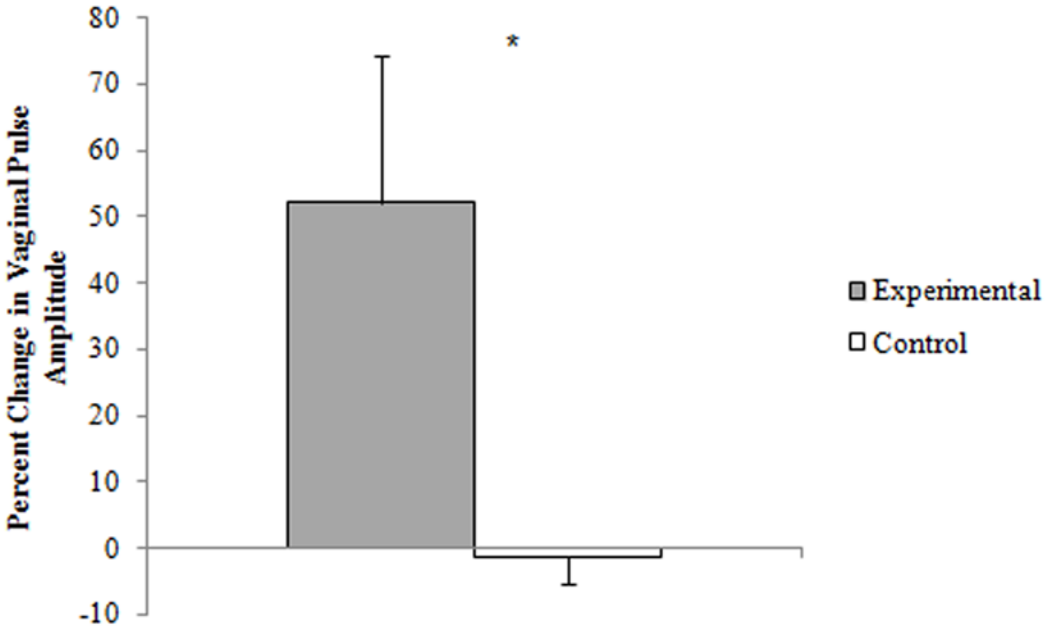


**Figure 1.**
Effects of film stimuli on vaginal pulse amplitude (VPA) percent change scores (neutral to erotic) in the experimental and control conditions. Data represent means ± SEM.
*$p < .05$, comparing the experimental to the control condition.

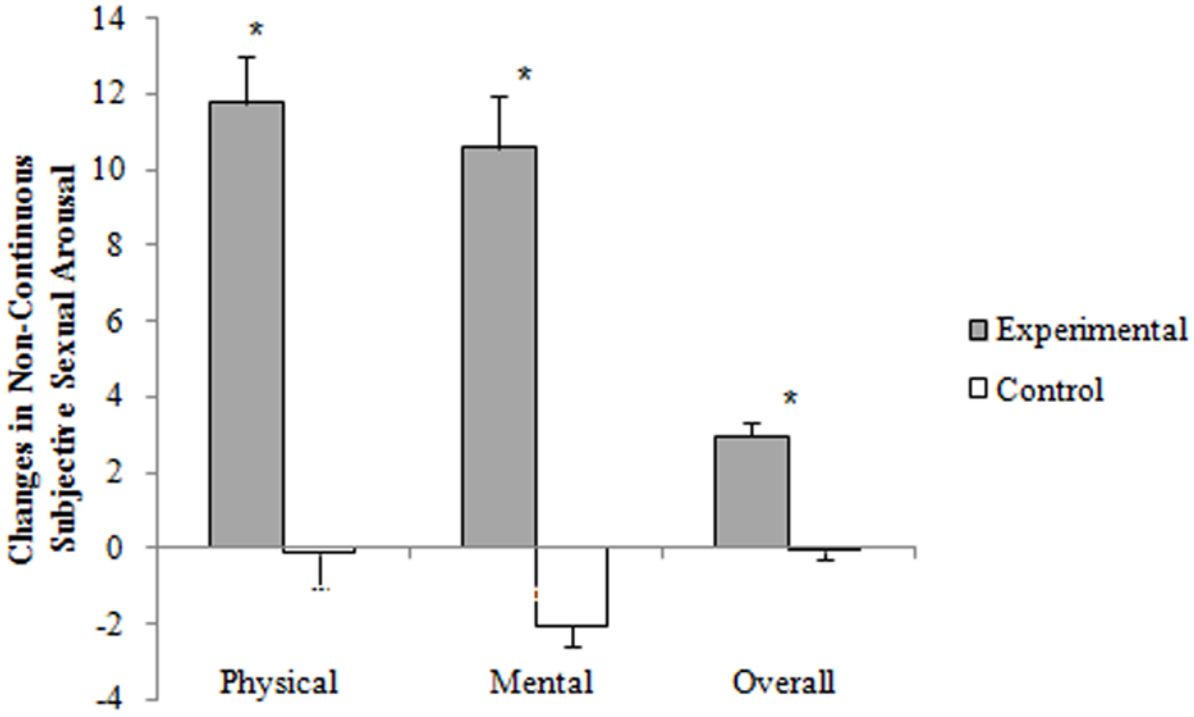


**Figure 2.**

Effects of film stimuli on indices of non-continuous subjective sexual arousal (subjective physiological sexual arousal, mental sexual arousal, and overall subjective sexual arousal) in the experimental and control conditions. Data represent means ± SEM.

*$p < .05$, comparing the experimental to the control condition.

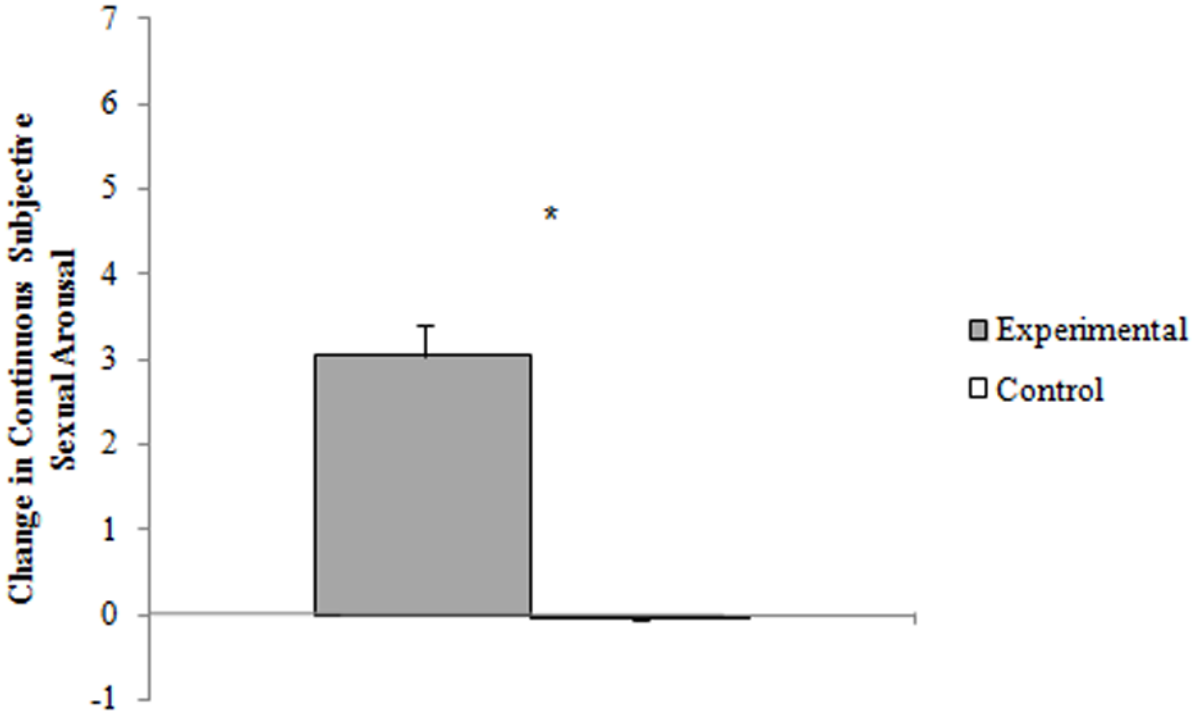


**Figure 3.**
Effects of film stimuli on continuous subjective sexual arousal in the experimental and control conditions. Data represent means ± SEM.
*$p < .05$, comparing the experimental to the control condition.

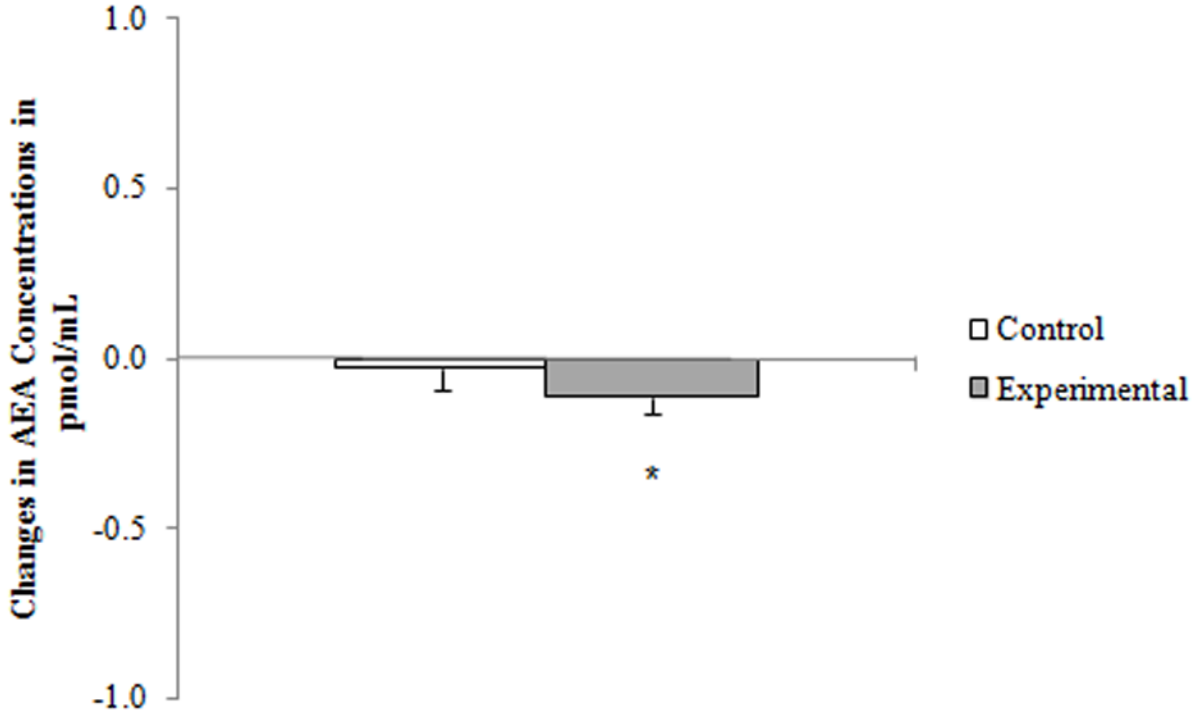


**Figure 4.**
Effects of film stimuli on AEA concentrations in the experimental and control conditions. Data represent means ± SEM.
*$p < .05$, comparing pre-film to post-film concentrations.

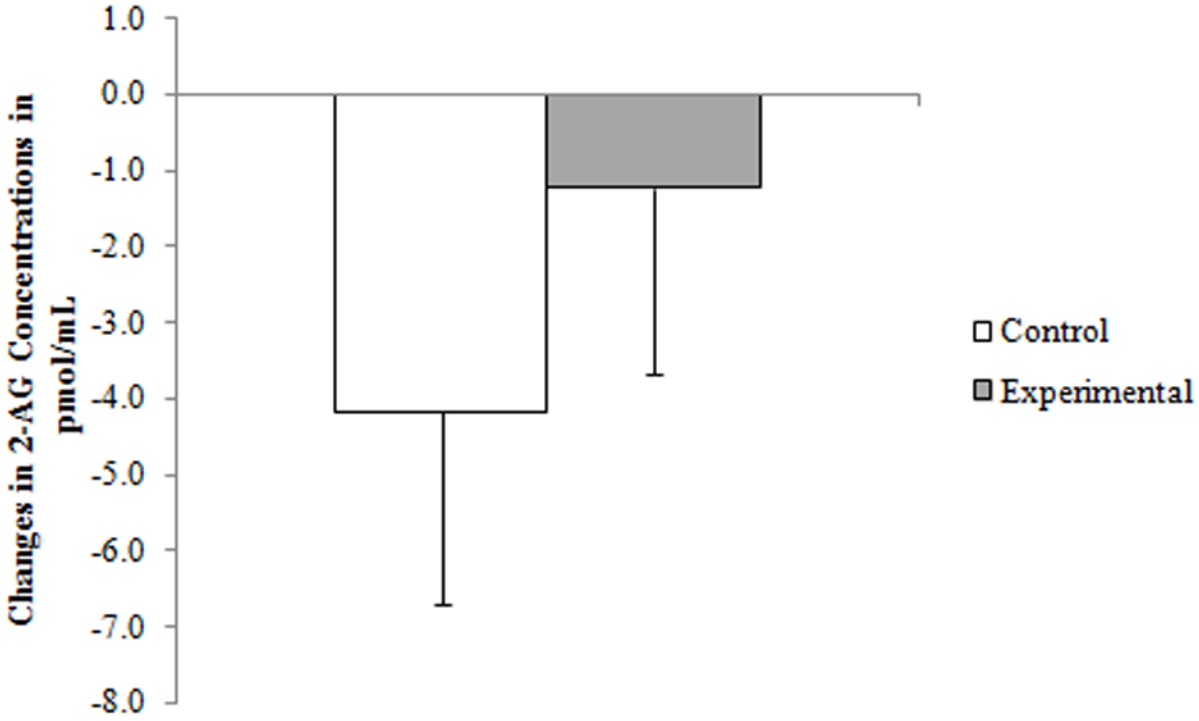


**Figure 5.**
Effects of film stimuli on 2-AG concentrations in the experimental and control conditions. Data represent means ± SEM.

**Table 1**

Participant Characteristics (N = 21)

| | **Mean (*SD*)** | **Range** | ***n* (%)** |
|---|---|---|---|
| Age | 25.33 (5.09) | 20-40 | |
| Years of Education | 15.95 (1.16) | 14-18 | |
| Ethnicity | | | |
| Caucasian | | | 11 (52.4) |
| East Asian | | | 8 (38.1) |
| South Asian | | | 1 (4.8) |
| Afro-Canadian | | | 1 (4.8) |
| Relationship Status | | | |
| Single | | | 8 (38.1) |
| Committed Relationship | | | 11 (52.4) |
| Married | | | 2 (9.5) |

## Table 2

Mean and Standard Deviation Pre- and Post-Film Endocannabinoid Concentrations

| | EXPERIMENTAL | | CONTROL | |
|---|---|---|---|---|
| | PRE *M* (*SD*) | POST *M* (SD) | PRE *M* (*SD*) | POST *M* (*SD*) |
| AEA | 0.91 (0.34) | 0.79 (0.30) | 0.94 (0.33) | 0.91 (0.47) |
| 2-AG | 32.08 (13.69) | 30.85 (16.03) | 36.08 (18.67) | 31.91 (15.89) |

*Note*. EXPERIMENTAL = experimental condition; CONTROL = control condition; AEA = arachidonoylethanolamide; 2-AG = arachidonoylglycerol; PRE = immediately prior to presentation of film stimuli; POST = immediately following presentation of film stimuli. *M* = Mean; *SD* = Standard Deviation. Values are presented in pmol/mL.

**Table 3**

Means, Standard Deviations, and Correlations for the Relationship Between Changes in Endocannabinoids and Changes in Physiological and Subjective Sexual Arousal

| EXPERIMENTAL CONDITION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variables** | **2-AG** | **VPA** | **PHYS** | **MEN** | **OVER** | **CON** | ***M*** | ***SD*** |
| AEA | .49* | -.48* | -.38 | -.51* | -.43^ | -.60* | -0.12 | .21 |
| 2-AG | — | -.17 | -.54* | -.33 | -.66* | -.63* | -1.22 | 11.23 |
| VPA | — | — | .04 | .27 | .29 | .46* | 52.10 | 101.99 |
| PHYS | — | — | — | .55* | .77* | .43^ | 11.76 | 5.66 |
| MEN | — | — | — | — | .77* | .34 | 10.57 | 6.20 |
| OVER | — | — | — | — | — | .61* | 2.95 | 1.75 |
| CON | — | — | — | — | — | — | 3.03 | 1.59 |
| CONTROL CONDITION | | | | | | | | |
| Variables | 2-AG | VPA | PHYS | MEN | OVER | CON | *M* | *SD* |
| AEA | .43^ | -.03 | .08 | .25 | -.00 | -.26 | -0.03 | .30 |
| 2-AG | — | -.43^ | -.12 | -.32 | -.10 | -.40 | -4.17 | 11.62 |
| VPA | — | — | -.11 | .23 | -.34 | -.18 | -1.25 | 18.36 |
| PHYS | — | — | — | .30 | .93* | .15 | -0.14 | 4.33 |
| MEN | — | — | — | — | .25 | .03 | -2.05 | 2.58 |
| OVER | — | — | — | — | — | .24 | -0.05 | 1.07 |
| CON | — | — | — | — | — | — | -0.03 | 0.16 |

*Note*. AEA = arachidonoylethanolamide; 2-AG = 2-arachidonoylglycerol; VPA = vaginal pulse amplitude; PHYS = non-continuous subjective physiological sexual arousal; MEN = non-continuous mental sexual arousal; OVER = non-continuous overall subjective sexual arousal; CON = continuous subjective sexual arousal.

* $p < .05$

^ $p < .06$