THE ENDOCANNABINOID SYSTEM AND FEMALE SEXUAL AROUSAL

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Abstract

Evidence from several lines of research points to the potential role of the endocannabinoid system in female sexual functioning. This evidence includes 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 the 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. However, while these lines of research are suggestive of a role of the endocannabinoid system in female sexual functioning, no studies investigating the relationship between levels of endogenous cannabinoids (i.e., arachidonoylethanolamide [anandamide or AEA] and 2-arachidonoylglycerol [2-AG]) and sexual functioning, or investigating the effects of exogenous cannabinoid use on physiological measures of sexual functioning in humans, have been conducted. Experiments 1 and 2 of the present dissertation are the first known studies to measure and examine circulating endocannabinoid levels in relation to both subjective and physiological indices of sexual arousal in women. Experiment 3 is the first known study to examine the relationship between exogenous cannabinoid use and physiological sexual arousal in women. Physiological sexual arousal in all three studies was measured via the vaginal photoplethysmograph. Although the results of Experiment 1 did not reveal an association between endocannabinoid levels and female sexual arousal, the results of Experiment 2 revealed a significant relationship, whereby increases in both physiological and subjective indices of sexual arousal were significantly associated with decreases in endocannabinoid (AEA and/or 2-AG) levels. Experiment 3 revealed that women who use marijuana show significantly smaller

increases in physiological sexual arousal in response to erotic film stimuli than women who do not use marijuana. The findings from these studies support the hypothesis that the endocannabinoid system plays a role in female sexual functioning. This line of research has broad clinical and research implications, not only in terms of furthering understanding of the biological mechanisms underlying female sexual functioning, but also in terms of finding effective treatments for sexual dysfunctions in women.

Preface

The research presented in this thesis was approved by the University of British Columbia Clinical Research Ethics Board and was covered by certificates H07-01675 (Experiment 1), H08-00150 (Experiment 2), and H08-01145 (Experiment 3).

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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, particularly in comparison to research on sexual functioning in men. Whereas the physiology underlying male sexual functioning is now relatively well discerned, resulting in significant advances in the medical treatment and management of various male sexual dysfunctions (Leite, Giachini, Carneiro, Nunes, Tostes, & Webb, 2007; Waldinger, 2007), the physiological mechanisms underlying female sexual functioning remain poorly understood. Numerous studies have attempted to find pharmacological treatments for female sexual dysfunctions (e.g., Basson & Brotto, 2003; Basson, McInnes, Smith, Hodgson, & Koppiker, 2002; Berman, Berman, Toler, Gill, & Haughie, 2003; Caruso, Agnello, Intelisano, Farina, Di Mari, & Cianci, 2004; Caruso, Intelisano, Lupo, & Agnello, 2001); however, null or inconsistent findings across studies have hindered further development of these agents. In fact, while there are multiple Food and Drug Administration (FDA) approved treatments for various male sexual dysfunctions, at the present time there is only one FDA approved medical treatment for a female sexual dysfunction (Food and Drug Administration, 2000). Furthermore, the one FDA approved medical treatment—the EROS clitoral therapy device (EROS-CTD) for female sexual arousal disorder—is not a pharmacological agent[1], underscoring the current lack of understanding of the physiological processes underlying female sexual functioning.

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

[1] The EROS-CTD is a small vacuum pump which is placed over the clitoris in order to increase blood flow and thus enhance physiological sexual arousal through clitoral engorgement.

endocannabinoid system in sexual behaviour (Gorzalka & Hill, 2006; Gorzalka, Hill, & Chang, 2010). The endocannabinoid system is a complex system in the brain and periphery made up of cannabinoid (CB) receptors, their endogenous ligands (termed endocannabinoids), proteins involved in the synthesis and breakdown of endocannabinoids, and the intracellular signalling pathways affected by cannabinoids (De Petrocellis, Cascio, & Di Marzo, 2004). Discovery of the central endocannabinoid system was the direct result of research investigating the physiological mechanisms of action of cannabis on the brain.

Overview of the Endocannabinoid System

The first exogenous, herbal cannabinoids (including Δ^9-tetrahydrocannabinol [THC], the active chemical compound in the cannabis plant) were identified and isolated in the 1960s (Isabell, Gorodetzsky, Jasinski, Claussen, von Spulak, & Korte, 1967; Mechoulam & Gaoni, 1965). The isolation of these exogenous, herbal cannabinoids led to the search for endogenous binding sites, and in 1988 Devane and colleagues published their work revealing the presence of high-affinity cannabinoid receptor binding sites in the rat brain (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988). Two cannabinoid receptors are now recognized: the CB_1 and CB_2 receptors.

CB_1 receptors are abundant in the mammalian brain, particularly in areas such as the hypothalamus, hippocampus, cerebellum, amygdala, striatum, throughout the cortex, and in the outflow nuclei of the basal ganglia (Herkenham, Lynn, Johnson, Melvin, de Costa, & Rice, 1991; Herkenham, Lynn, Little, Johnson, Melvin, de Costa, et al., 1990; Rodríguez de Fonseca, Cebeira, Ramos, Martin, & Ferdandez-Ruiz, 1994; Tsou, Brown, Sanudo-Pena, Mackie, & Walker, 1998). CB_1 receptors are also found in peripheral tissues including the gastrointestinal

tract, liver, pancreas, and adipose tissue (Cota & Woods, 2005; Juan-Picó, Fuentes, Bermúdez-Silva, Javier Díaz-Molina, Ripoll, Rodríguez de Fonseca, et al., 2006; Pagotto, Marsicano, Cota, Lutz, & Pasquali, 2006). These peripheral locations, along with the abundance of CB_1 receptors in the hypothalamus, have led researchers to examine the role of the endocannabinoid system in energy balance and homeostasis. It is now known that the endocannabinoid system plays a critical role in these two biological processes, particularly with regard to controlling appetite and food intake (Cota, Marsicano, Tschöp, Grübler, Flachskamm, Schubert, et al., 2003; Di Marzo & Matias, 2005). It is primarily for this reason that the desire to consume high-caloric foods following cannabis use exists. Similarly, the high density of CB_1 receptors in the hypothalamus and the pituitary gland has led researchers to propose that activation of the endocannabinoid system modulates the hypothalamic-pituitary-adrenal (HPA) axis, thereby suggesting a role for the endocannabinoid system in the stress response (Gorzalka, Hill, & Hillard, 2008). In contrast, the CB_2 receptor is mainly localized in peripheral tissues including the spleen, thymus, and immune and hematopoietic cells, and appears to play a role in immune function (Demuth & Molleman, 2006). At present, there is no compelling evidence to suggest a behavioural role for CB_2 receptors.

In 1990, the first endogenous cannabinoid (or "endocannabinoid"), arachidonoylethanolamide (AEA), also known as anandamide, was discovered (Devane, Hanus, Breuer, Pertwee, Stevenson, Griffin, et al., 1992). This was followed three years later by the discovery of a second endocannabinoid, 2-arachidonoylglycerol (2-AG; Sugiura, Kondo, Sukagawa, Nakane, Shinoda, Itoh, et al., 1995). While 2-AG has a high affinity to both CB_1 and CB_2 receptors and is a full CB_1 receptor agonist, AEA is only a partial CB_1 receptor agonist

(Sugiura, Kodaka, Nakane, Miyashita, Kondo, Suhara, et al., 1999). Other ligands have also been postulated as potential endocannabinoids, including N-docosatetraenoylethanolamine, N-dihomo-γ-linolenoylethanolamine, N-arachidonoyl dopamine, O-arachidonoylethanolamine (virodhamine), oleamide, and N-oleoyl dopamine (see Pertwee, 2005), although their status as endocannabinoids remains under investigation and is not currently conclusive.

AEA and 2-AG are synthesized on demand (as opposed to being produced in advance and being stored in vesicles) following depolarization of post-synaptic cells, increases in intracellular calcium, and/or activation of various phospholipase enzymes. Following synthesis, AEA and 2-AG are discharged into the synapse by the post-synaptic cell, from where they activate cannabinoid CB_1 receptors located on axon terminals of the pre-synaptic cell. Activation of cannabinoid receptors inhibits the release of neurotransmitters from the pre-synaptic cell. Specifically, cannabinoid binding by both AEA and 2-AG to the CB_1 receptor results in the inhibition of the release of dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate, and acetylcholine (Schlicker & Kathmann, 2001). It is through activation of this receptor that THC elicits its psychopharmacological effects. The CB_2 receptor has been less thoroughly investigated, and its mechanism of action is at this time not well understood.

Following activation, AEA and 2-AG are removed via cellular uptake and metabolized by enzymes within the cell. AEA is metabolized by the enzymes fatty acid amide hydrolase (FAAH), cyclooxygenase-2, lipoxygenases, and cytochrome P450 (reviewed in Pertwee, 2008) while 2- AG is metabolized by monoacylglycerol lipase (MAGL) and FAAH (Dinh, Carpenter, Leslie, Freund, Katona, Sensi, et al., 2002).

Just as the effects of cannabis use and the localization of cannabinoid receptors led scientists to investigate the roles of the endocannabinoid system in appetite, energy, and metabolism, the effects of cannabis use and localization of cannabinoid receptors has also led to suggestions for the potential role of the endocannabinoid system in sexual behaviour (e.g., Gorzalka & Hill, 2006; Gorzalka et al., 2010). In fact, findings from several lines of research now point to the potential role of the endocannabinoid system in female sexual functioning: 1) evidence from the effects of cannabis/THC use on subjective indices of sexual function in humans; 2) evidence from the administration of exogenous cannabinoid agonists and antagonists on observable sexual behaviours 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.

Together, these findings suggest that the endocannabinoid system may play a role in female sexual behaviour. If so, the findings may lead not only to an enhanced understanding of the biological mechanisms underlying female sexual functioning, but also to potential progress in the treatment of female sexual difficulties. As female sexual difficulties have a high prevalence rate of around 40% (Laumann, Paik, & Rosen, 1999), the implications for sexual and relationship well-being, as well as for other factors affected by decreased sexual functioning such as mood, self-esteem, and anxiety, are significant.

Evidence from the Effects of Cannabis/THC Use in Humans

Although the Indian Hemp Drugs Commission (1894) believed that cannabis was detrimental to sexual function, cannabis has a long-standing reputation as a drug that enhances sexuality. For example, as reviewed by Abel (1981), cannabis has been viewed as an aphrodisiac across the globe and throughout the centuries, including hashish being credited with aphrodisiac properties in ancient Arab literature, marijuana being shunned during the Middle Ages because of its believed use as an aphrodisiac during the Witches' Sabbath, and marijuana being strongly associated with the Tantric religion in India, where it was believed to stimulate libido.

These beliefs about the enhancing effects of cannabis on sexual function appear to remain in place to the present day. For example, a study by Sumnall and colleagues revealed that over 30% of a sample of 270 adults in the United Kingdom who engaged in sexual activities following illicit drug use reported using cannabis purposely to enhance their overall sexual experiences, including the perceptual, emotional, sensual, and subjective experiences of sex (Sumnall, Beynon, Conchie, Riley, & Cole, 2007). Sixteen per cent reported using cannabis specifically to enhance sexual arousal or increase sexual desire/drive (Sumnall et al., 2007). Similarly, another study published one year later involving 1341 participants (650 males and 691 females) between the ages of 16–35 from nine different European countries, of which nearly three quarters had used marijuana, found that 29% of the females reported using cannabis in order to specifically enhance sexual sensations and arousal (Bellis, Hughes, Calafat, Juan, Ramon, Rodriguez, et al., 2008). Although not as recent, Bouguet (1950) stated that in North Africa and Egypt, the belief that marijuana enhances sexual satisfaction is one of the primary reasons many individuals initially use the drug.

Despite these longstanding and widespread beliefs about the impact of cannabis on sexual function, it was not until the late 1960s that researchers began to gather empirical data on the effects of cannabis use on sexual behaviour. The results have shown that both men and women report alterations in sexual experiences and functioning following cannabis use (e.g., Chopra & Jandu, 1976; Goode, 1969; Helikas, Weller, & Morse, 1982; Koff, 1974); however, while the results in men have been equivocal as to whether cannabis facilitates or inhibits sexual function (for reviews, see Gorzalka & Hill, 2006; Gorzalka et al., 2010), the results in women have almost consistently suggested a facilitatory effect.

Specifically, in the first study investigating the self-reported effects of cannabis use on sexual behaviour, Goode (1969) interviewed 200 male and female marijuana users and found that 50% of the women reported an increase in sexual desire following marijuana use (the comparable figure for men was 39%). Three years later, a National Commission on Marihuana and Drug Abuse (1972) opinion survey similarly concluded that women reported increases in sexual desire with cannabis use, and that they did so to a greater extent than did men.

Shortly thereafter, Koff (1974) conducted a study in which he set out to further investigate differences between men and women in their self-reported effects of marijuana on sexual experiences. In addition, Koff was interested in discerning the dosage of marijuana believed to produce the most pronounced sexual effects. His study involved mailing out 640 questionnaires to randomly chosen male and female students enrolled at eight major universities in the United States. Three hundred and forty-five questionnaires were returned, although data from 93 participants were discarded due to these individuals reporting no history of marijuana use. The final sample consisted of 128 females and 123 males. Via the questionnaire, participants

were asked three questions pertaining to sexual function while under the influence versus while not under the influence of marijuana: 1) whether their sexual desire increased, decreased, or remained the same; 2) whether their sexual enjoyment increased, decreased, or remained the same; and 3) whether their partner's satisfaction from sexual activity following marijuana use increased, decreased, or remained the same.

Koff (1974) found that, with respect to sexual desire, 58% of females reported an increase and only 5% reported a decrease in sexual desire following marijuana use (the respective percentages for males were 39% and 11%). With respect to sexual enjoyment, Koff found that 43% of females reported an increase, and that only 7% reported a decrease with marijuana use (percentages for males were 60% and 7%, respectively). Finally, with respect to their partner's satisfaction from sexual activity, 47% of female participants reported an increase with marijuana use and 9% reported a decrease (percentages for males were 60% and 4%, respectively). Overall, these results revealed that a majority of the females in the sample felt that marijuana resulted in increased sexual desire, and that significantly more females than males reported this effect. More females also reported that marijuana enhanced (versus decreased or did not change) their partner's satisfaction from sexual activity, although the number who indicated enhanced partner satisfaction was only slightly higher than the number who reported no change.

Finally, with respect to the effects of dose on sexual function, Koff (1974) found that 71% of females in his sample reported an increase in sexual desire after smoking no more than one marijuana joint but that this number dropped to 50% for females who smoked two or more joints. Thus, Koff concluded that as the marijuana dose increases beyond one marijuana joint, the beneficial effects of marijuana on sexual desire decrease. Similar results were found for self-

reported sexual enjoyment, with the number of women reporting increased sexual enjoyment after smoking more than one marijuana joint decreasing in relation to increased doses of marijuana.

In 1979, further research on the self-reported effects of cannabis on sexual function was published (Dawley, Winstead, Baxter, & Gay, 1979; Kolodny, Masters, & Johnson, 1979). Dawley and colleagues (1979) studied attitudes with respect to the effects of marijuana on sexual pleasure and satisfaction in 84 graduate students enrolled at an American medical centre. Thirty-three of their 84 participants (39%) reported having engaged in sexual activities while under the influence of marijuana, while 26 reported experiences using marijuana but never during sexual activities, and 25 reported no history of marijuana use. Dawley and colleagues referred to these three groups as experienced smokers, non-experienced smokers, and non-smokers, respectively. Participants were administered a 57-item true-false questionnaire that included 15 items from the Lie (L) scale of the Minnesota Multiphasic Personality Inventory (MMPI). The results of their study revealed that 88% of experienced smokers reported that using marijuana resulted in increased pleasure during intercourse, and 42% reported that using marijuana resulted in increased pleasure during oral sex. (Despite never having had sexual experiences while high, 77% of non-experienced smokers, and 52% of non-smokers, reported believing that marijuana use would increase sexual pleasure during intercourse, and 54% and 20%, respectively, believed this to be the case during oral sex). Fifty-eight per cent of experienced marijuana smokers in the study endorsed a question asking whether they believed marijuana increased the intensity of orgasm (with corresponding figures of 35% and 36% in non-experienced smokers and non-smokers, respectively). Finally, 61% of experienced smokers reported that they believed

marijuana was an aphrodisiac (corresponding figures for non-experienced smokers and non-smokers were once again 35% and 36%, respectively). In essence, those individuals who had engaged in sexual experiences while under the influence of marijuana consistently held positive views of the effects of marijuana on sexual function, and generally to a greater degree than did non-marijuana users or marijuana users who had never engaged in sexual activities while high.

Research published in the same year by Kolodny et al. (1979) involved 500 female participants and found that cannabis consumption resulted in subjective increases in sensitivity to touch and relaxation, which in turn were believed to result in increased sexual responsiveness. In fact, 81% of the women in this study reportedly indicated that marijuana improved their sexual experiences; however, in contrast to the previous findings by Goode (1969), Koff (1974), Dawley and colleagues (1979), and the National Commission on Marihuana and Drug Abuse (1972), this research did not find any significant effects of cannabis consumption on sexual desire, nor did this study find any effects of cannabis consumption on vaginal lubrication and either orgasm frequency or orgasm intensity (Kolodny et al., 1979).

Three years later, Halikas and colleagues published an interview-based study dating back to 1969 and 1970 that involved 100 regular marijuana users (61 men and 39 women) and 50 non-users (Halikas, Weller, & Morse, 1982). All of the marijuana users had used marijuana on at least 50 occasions over a minimum period of six months. Interviews included asking participants to complete a checklist of 105 items that consisted of potential marijuana effects (both sexual and non-sexual) that had previously been reported in the literature. The researchers found that 40% of marijuana-using women in their sample reported that marijuana improved their orgasmic functioning and 90% reported overall enhanced sexual pleasure and satisfaction (Halikas et al.,

1982). Of note is the fact that these authors re-interviewed 97 of the original 100 marijuana users 6–8 years later, and found that the perceived beneficial effects of marijuana on sexual functioning were maintained over this period of time (Halikas, Weller, Morse, & Hoffman, 1985).

Not in contradiction to these self-reported positive effects of cannabis on sexual function is a recent study by Smith and colleagues (Smith, Ferris, Simpson, Shelley, Pitts, & Richters, 2010). This study involved computer-assisted telephone interviews with 4350 women between the ages of 16 and 64, and queried specifically for sexual difficulties of at least one month's duration including low sexual desire, orgasmic dysfunction, sexual pain, not finding sex pleasurable, lack of vaginal lubrication, and anxiety about sexual performance. The results of this study did not indicate a correlation between sexual difficulties and frequency of cannabis use.

In contrast to the findings of Smith and colleagues (2010), however, a previous study by Johnson and colleagues did report negative effects of cannabis use on female sexual functioning (Johnson, Phelps, & Cottler, 2004). Specifically, this study, which consisted of an analysis of data collected as part of the Epidemiological Catchment Area (ECA) study of mental illness in St. Louis from 1981 to 1983 (Eaton & Kessler, 1985; Robins & Regier, 1991), examined associations between sexual dysfunctions (inhibited sexual desire, sexual excitement, and orgasm, as well as painful sex) and substance use. The study involved 3004 non-institutionalized men and women, of whom 60% were female. Analyses controlled for psychiatric disorders, health status, and demographic variables. The results revealed that inhibited orgasm and painful sex were both independently associated with a history of marijuana use.

One other study that deserves mention is a study conducted by Tart in 1970 which assessed the self-reported effects of marijuana on sexual function (among other outcomes); however, Tart did not analyze his results by gender. As a result, the extent to which his findings pertain to women versus men is unknown. His study involved 153 male and female college students who had used marijuana at least a dozen times prior to study participation, and revealed that a significant percentage of his sample endorsed beneficial effects of marijuana on sexual function. Specifically, in addition to other reported beneficial sexual effects of marijuana, 77% of his sample endorsed a question asking whether marijuana at least sometimes led to orgasms having new, pleasurable qualities, and 66% of his sample endorsed a question asking whether marijuana at least sometimes resulted in an increased sex drive or a greater need for sex.

While these studies are suggestive of a possible link between cannabis use and sexual function (and, in fact, with the exception of the Johnson et al. [2004] study, suggestive of a *positive* association between cannabis and female sexual function), the data in these studies are based solely on self-report. Further, the terminology relating to sexual functioning has not only varied across these studies but has also not been fully articulated and defined. Studies noted above have referred to increases in "sexual pleasure" or "satisfaction"; however, it is unclear to what these terms are specifically referring. For example, do these terms refer to increased ease or frequency of experiencing orgasm leading to increased satisfaction, increased genital responsivity in the form of genital lubrication leading to increased pleasure during sexual activity, increases in the subjective perception of the sexual encounter independent of physiological function, increased sexual desire, or some combination of these factors which influence the sexual experience?

It also must be recognized that numerous other explanations, besides a direct association between the endocannabinoid system and sexual functioning, may account for the self-reported effects of cannabinoids on sexuality in women. For example, it may be that cannabis alters either sensation and/or perception in such a way that sexual experiences are enhanced (Abel, 1981; Adams & Martin, 1996). In fact, Halikas et al. (1982) proposed that cannabis exerts its effects on sexual functioning via increased tactile sensitivity. In support of this, a participant in the study by Koff (1974) reportedly noted, "sex is different since some sensations are seemingly heightened by the drug," (p. 198). Further, in the study by Dawley and colleagues (1979), 48% of experienced marijuana users reported that marijuana had a positive effect on sensations during sexual intercourse.

Alternatively, sexual function may be enhanced indirectly through the effects of cannabinoids on anxiety. The anxiolytic effects of cannabis are well known (Adams & Martin, 1996; Hathaway, 2003), and it may be that as a result of these anxiolytic effects, women are more able to relax and enjoy the sexual encounter and, thereby, also experience enhanced sexual functioning. In fact, these alternative explanations have some support in the literature. For example, Kolodny and colleagues (1979) found that while 81% of their sample of 500 women reported that cannabis use resulted in enhanced sexual pleasure, this pleasure was attributed to the effects of increased relaxation and tactile sensitivity on sexual responsiveness—not to any direct effects of cannabis on sexual desire, arousal, or orgasmic functioning. At the same time, it is interesting to note that a study by Reese (1977) found that marijuana resulted in either negative or no effects on tactile sensitivity in nonsexual situations, leading to doubts that marijuana would lead to increased tactile sensitivity in sexual contexts.

Another possible reason that individuals may link cannabis use to perceived enhancements in sexual function may be due to a slowing of temporal perception while high, such that sexual activities are perceived to last longer than is actually the case (Jarvik & Brecher, 1977; Melges, Tinklenberg, Hollister, & Gillespie, 1971). Melges et al. (1971) note that slowing of temporal perception can also be accompanied by increased concentration on the present moment. Awareness of the present moment and mindfully focusing on the body and its sensations during sexual activity are linked to enhanced sexual functioning. In fact, two recent uncontrolled trials have found significant beneficial effects of mindfulness-based cognitive behavioural therapy for women with sexual desire and arousal difficulties (Brotto, Basson, & Luria, 2008; Brotto, Heiman, Goff, Greer, Lentz, Swisher, et al., 2009). Related to this, the effects of cannabis on temporal perception and concentration are also believed to promote sensate focus[2] and, in turn, sexual pleasure, by fostering an erotic experience of the entire body as opposed to specific erogenous zones (Gawin, 1978; Lewis, 1970).

Another possibility is that cannabis results in disinhibition, which in turn, allows for increased relaxation and sensory focus (Dawley et al., 1979; Kolodny et al., 1979; McKay, 2005). For example, Kolansky and Moore (1972) reported that cannabis use resulted in a period of sexual disinhibition in some women. Koff (1974) discussed that cultural roles for women have resulted in women often repressing their sexual desires and that marijuana's "lessening of tensions and inhibitions allows the women to overcome these concepts and to express her desires," (p. 198). In support of this, one of Koff's (1974) female participants noted, "...the

[2] Sensate focus is a technique developed by Masters and Johnson (1970) that is designed to reduce "spectatoring"—focusing on oneself from a third person perspective, which is associated with increased performance anxiety—by increasing relaxation and focusing on one's senses during sexual activities, and eliminating any focus on sexual performance.

closeness of someone's body while stoned gives me a sense of security and uniqueness. Weed decreases my inhibitions allowing me to express more affection and give more to my partner's enjoyment," (p. 200).

Finally, it is also entirely plausible that the perceived positive effects of cannabis on sexual function reported in the human literature are due purely to expectancy effects (i.e., a placebo effect), given cannabis' longstanding reputation as an aphrodisiac. Some literature supports the idea that marijuana users' sexual experiences are influenced by their sexual expectations of the substance, as well as by the setting, personality, age, and relationship status of the user (Crenshaw & Goldberg, 1996; Rosen, 1991). In other words, the perceived relationship between cannabis and sexual outcomes may be purely correlational, with cannabis having neither direct nor indirect effects on sexual function.

A spurious correlation between cannabis and sexual function may be the result of the fact that alcohol and other psychoactive substances are often taken in conjunction with cannabis. These other substances may affect subjective and/or physiological sexual function but the effects may erroneously be attributed to cannabis. Alternatively, the situations in which cannabis use most often occur may be the same situations that are most conducive to optimal sexual function—situations in which individuals feel relaxed and less sexually constrained. This notion is supported by one of the participants in Koff's (1974) study, who stated: "Marijuana itself does not in any way increase sexual desire. It is merely the atmosphere in which the drug is used combined with the drug...a darkened room with candlelight, incense burning possibly, often just the two alone, which actually promotes sexual desire," (p. 196).

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, shown a facilitatory effect, 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, particularly research using physiological measures of sexual functioning.

Evidence from Cannabinoid Administration in Other Species

Although no published research to date has employed physiological measures to examine the effects of cannabis use on sexual function in women, studies of observable sexual behaviours in non-human species provide further support for the hypothesis that the endocannabinoid system may be implicated in the physiology of female sexual behaviour. In line with the results cited above by Koff (1974) of a dose-dependent effect of cannabis on sexual function in women, the effects of cannabis on sexual behaviour in the female rodent have also shown a dose-dependent effect, with high doses impairing lordosis (a receptive sexual behaviour involving arching of the back, raising of the rump, and moving of the tail to one side to facilitate copulation) but the opposite, facilitatory effect occurring at low doses (Gordon, Bromley, Gorski, & Zimmerman, 1978).

While not examining the effects of dose, Turley and Floody (1981) and Mani, Mitchell, and O'Malley (2001) similarly found that THC resulted in enhanced sexual receptivity in female hamsters and rats, respectively. In addition, Turley and Floody (1981) also investigated sexual proceptivity (female behaviour which serves to attract a male and increase the probability that he will mount the female) and found that THC had a facilitatory effect on this behaviour as well.

Thus, both sexual proceptivity and receptivity appear to be enhanced, at least at lower doses, following cannabis administration in female rodents. Consistent with this conclusion, Mani and colleagues (2001) also examined the effects of the cannabinoid antagonist SR141716A and found it to significantly diminish sexual receptivity.

While these results provide more empirical support for the potential role of the endocannabinoid system in female sexual functioning, three studies have produced findings which are in contrast to those reviewed above. First, Ferrari, Ottani, and Giuliani (2000) found that acute administration of the potent cannabinoid agonist, HU-210, attenuated, rather than facilitated, sexual receptivity in the female rat. Second, López, Webb, and Nash (2009) found that the CB_1 receptor antagonist/inverse agonist, AM251, significantly increased, rather than decreased, sexual motivation, receptivity, and proceptivity in the female rat. Third, López, Zappie, Cushman, and Chadwick (2010) found that, similar to the findings of Ferrari et al. (2000) with the cannabinoid agonist HU-210, the CB_1 receptor agonist, CP55,940, attenuated rather than facilitated sexual motivation in female rats. The latter result was dose-dependent, with a 40 μg/kg dose of CP55,940 being associated with a more significant decrease in sexual motivation than a 20 μg/kg dose. It should also be noted that the 40 μg/kg dose also resulted in a decrease in social motivation for a conspecific female, meaning that at higher doses, the effects of CP55,940 were not found to be specifically sexual. Nonetheless, based on these findings, López and colleagues (2009, 2010) suggested that endocannabinoids play an inhibitory, rather than a facilitatory, role in the regulation of female sexual behaviours in the rat.

It is possible that the contradictory findings between these various animal studies are due to the different pharmacological properties of HU-210, CP55,940, and AM251, and/or to the

methodologies employed in these studies. HU-210 and CP55,940 are very potent synthetic cannabinoid receptor agonists. The study by Ferrari et al. (2000) found that HU-210 at doses of 25, 50, and 100 μg/kg reduced lordosis quotients, lordosis ratings, and proceptive behaviours, and the study by López et al. (2010) found that CP55,940 at doses of 20 and 40 μg/kg reduced sexual motivation in female rats. Specifically, both sets of researchers found a negative relationship between dose and sexual behaviour, with increasing doses of HU-210 and CP55,940 resulting in decreasing effects on sexual behaviour; however, as HU-210 and CP55,940 are very potent[3], it is possible that even the lowest doses of HU-210 and CP55,940 used by Ferrari et al. (2000) and López et al. (2010), respectively, acted in a manner similar to high doses of THC in the research by Gordon et al. (1978). The latter research revealed that high doses of THC impaired, but low doses facilitated, female sexual function. (Impairment at high doses is common in the cannabinoid literature due to consequent effects on motor activity and, in fact, López and colleagues [2010] acknowledged these known motor effects in their publication.) Therefore, the findings by Ferrari et al. (2000) and López et al. (2010) may, in fact, *not* be contradictory to research which has found that cannabinoid agonists at low doses facilitate female sexual behaviour; however, without research investigating the effects of lower doses of HU-210 and CP55,940 on sexual behaviour than those administered by Ferrari et al. (2000) and López et al. (2010), respectively, this remains speculative.

With respect to AM251, in vitro studies have found that at lower doses, this substance acts as an antagonist, but at higher doses may exhibit inverse agonist activity (Pertwee, 2005).

[3] HU-210 has been found to be seven-fold more potent that THC (Howlett, Champion, Wilken, & Mechoulam, 1990) and CP55,940 has been found to be 45 times more potent than THC (Thomas, Gilliam, Burch, Roche, & Seltzman, 1998).

López and colleagues (2009) intentionally employed doses of AM251 which they believed were indicative of inverse agonist activity; however, as discussed, if high doses of cannabinoids inhibit sexual behaviour, then high doses of AM251, acting as a cannabinoid inverse agonist, may explain the positive effects on sexual behaviour which López et al. (2009) found. Nonetheless, without research investigating the effects of lower doses of AM251 in comparison to higher doses, this also remains speculative.

With respect to the discrepancy between the results of López et al. (2009) and Mani et al. (2001) of the effects of cannabinoid antagonists on sexual behaviour, the discrepancy may be the result of several methodological differences. First, the rats in the Mani et al. (2001) study were administered 2 μg of estradiol benzoate subcutaneously and 2 μg of progesterone via intracerebroventricular injections, whereas those in the López et al. (2009) study were administered much higher doses of estradiol benzoate and progesterone systemically. The delivery of the cannabinoid antagonist also differed in that it was administered centrally in the study by Mani et al. (2001), but peripherally in the López et al. (2009) study. Mani et al. (2001) and López et al. (2009) also used different methods to assess sexual receptivity; while Mani et al. (2001) utilized a non-paced mating procedure, López et al. (2009) used a paced mating chamber that allowed the female to dictate the frequency of copulation and is associated with less female aversion to mating (Martínez & Paredes, 2001). Finally, López`s (2009) team delivered the cannabinoid antagonist AM251 whereas Mani et al. (2001) administered the cannabinoid antagonist SR141716A. This is an especially notable methodological difference given that some physiological effects have been shown to be only elicited by SR141716A and not AM251 (Ford, Honan, White, & Hiley, 2002).

Given these contradictory findings between studies, the role of the endocannabinoid system in female rodent sexual behaviour 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. There are significant differences between the hormonal mechanisms implicated in non-human versus human sexual behaviour. Specifically, in female rodents, estradiol and progesterone are the two hormones implicated in sexually proceptive and receptive behaviours, whereas in human females, androgens have been implicated (see Motofei and Rowland, 2005; van Anders, Chernick, Chernick, Hampson, & Fisher, 2005); however, there is no reason to assume that this would, necessarily, be a confound in cross-species comparisons of the role of endocannabinoids in sexual function. Research examining the effects of THC on rodent sexual behaviour has shown that the facilitatory effects of THC are not dependent on either estrogen- or progesterone-related mechanisms (Gordon et al., 1978; Turley & Floody, 1981). In fact, Mani and colleagues (Mani et al., 2001) found that sexual receptivity was facilitated by intracerebroventricular administration of THC in estrogen-primed female rats and resulted specifically from the activation of CB_1 receptors by THC. Therefore, the effects of cannabinoids on sexual behaviour do not appear to be specific to any direct effects on ovarian hormones; rather, it appears that the effects are at least partially mediated by the central nervous system, leaving open the possibility that the mechanisms leading to facilitated sexual functioning in rodents may also be similar in humans.

Nevertheless, without research that attempts to understand and reconcile the contradictory findings above (findings which are more contradictory than those in the human literature previously summarized), and without research employing physiological measures in

human females, no definitive conclusions regarding the role of the endocannabinoid system in female sexual behaviour can be made.

The Location of Cannabinoid Receptors in the Brain and Other Tissues

As previously described, 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 (Herkenham et al., 1990, 1991; Rodríguez de Fonseca et al., 1994; Tsou et al., 1998). As discussed by Gorzalka et al. (2010), the distribution of cannabinoid receptors throughout these brain structures positions this system to modulate sexual behaviour through a number of possible mechanisms: First, activation of cannabinoid CB_1 receptors located within the striatum and cerebellum results in motor incoordination and decreased motor activity (DeSanty & Dar, 2001; Egashira, Mishima, Iwasaki, & Fujiwara, 2002; Patel & Hillard, 2001; Lichtman, Cook, & Martin, 1996). As a result, cannabinoids may, in part, exert effects on sexual functioning through changes in motor function.

Second, CB_1 receptors located within corticolimbic structures such as the prefrontal cortex, amygdala, and hippocampus regulate emotional behaviour and responses to stress (Hill McLaughlin, Morrish, Viau, Floresco, Hillard, et al., 2009; McLaughlin, Hill, Morrish, & Gorzalka, 2007; Rubino, Guidali, Vigano, Realini, Valenti, Massi, et al., 2008). Thus, cannabinoids may also, in part, exert indirect effects on sexual functioning by modulating the expression of stress and anxiety.

Third, activation of CB_1 receptors located within the dorsal raphe in the brainstem and ventral tegmental area in the midbrain—brain tissues that contain cell bodies for the serotonergic (dorsal raphe) and dopaminergic (ventral tegmental area) input to the forebrain—may modulate

the synaptic release of these neurotransmitters, both of which are highly implicated in the regulation of genital reflexes, and sexual motivation and inhibition (Hull, Muschamp, & Sato, 2004; Matyas, Urban, Watanabe, Mackie, Zimmer, Freund, & Katona, 2008). Thus, the endocannabinoid system may modulate sexual function through direct effects on the release of serotonin and dopamine.

Finally, as previously noted, cannabinoid receptors are located within the hypothalamus—a structure critical in mediating sexual behaviour. The hypothalamus releases hormones to the anterior pituitary, which in turn releases tropic hormones which further influence the release of sex steroids (androgens and estrogens) and other hormones from endocrine glands including the gonads and adrenal cortex. Studies have shown that when certain parts of the hypothalamus are destroyed, dramatic reductions in both male and female sexual behaviours can result (Hitt, Hendricks, Ginsberg, & Lewis, 1970; Law & Meagher, 1958; for a review, see Paredes & Baum, 1997). Given the density of cannabinoid receptors in the hypothalamus, and the recently discovered relationship between the endocannabinoid system and other functions controlled by the hypothalamus (such as energy balance and food intake) it is highly plausible that cannabinoid receptor activation also influences hypothalamic functions critical in sexual behaviour. Specifically, within the hypothalamus, CB_1 receptors are distributed throughout neuropeptide populations and are known to regulate the release of numerous peptides that are known to be important for sexual activity, physiology, and reproduction, including oxytocin (Gorzalka & Lester, 1987; Sabatier and Leng, 2006) and gonadotropin releasing hormone (Gammon, Freeman, Xie, Petersen, & Wetsel, 2005). Thus, cannabinoids may

modulate sexual function through direct effects on the network of peptide neurons in the hypothalamus.

In addition to high densities in the brain, cannabinoid receptors are also present in peripheral tissues, including reproductive tissues such as the ovaries (Geliegue, Mary, Marchand, Dussossoy, Carriere, Carayon, et al., 1995), which are a major source of both estrogens and androgens. Estrogens play a role in vaginal lubrication, a part of the physiological sexual arousal response. Moreover, in studies examining the effects of estrogen-replacement therapy (ERT), estrogens have been associated with increased sexual desire, pleasure, and orgasmic capacity (Dennerstein, Burrows, Wood, & Hyman, 1980; Dow, Hart, & Forrest, 1983), although some have argued that the sexual benefits of estrogens occur more as a result of the effects of estrogens on mood than on biological processes relating to sexual functioning (e.g., Crenshaw, 1996), and other researchers have found that estrogens at high doses may actually decrease sexual desire (Graham, Ramos, Bancroft, Maglaya, & Farley, 1995; Myers, Dixen, Morrissette, Carmichael, & Davidson, 1990; Redmond, 1999). A somewhat less contradictory role in female sexual function exists for testosterone, the major gonadal androgen. Studies have shown a relationship between levels of circulating testosterone and sexual desire (Bartlik, Kaplan, Kaminetsky, Roentsch, & Goldberg, 1999; Davis, McCloud, Strauss, & Burger, 1995; Gelfand, 2000; Yates, 2000; van Anders et al., 2005), as well as between testosterone and physiological sexual arousal (Tuiten, Van Honk, Koppeschaar, Bernaards, Thijssen, & Verbaten, 2000), although low testosterone and testosterone metabolites have not been found to significantly differentiate women with and without hypoactive sexual desire disorder (Basson, Brotto, Petkau, & Labrie, 2010).

As with the hypothalamus, the presence of cannabinoid receptors in the reproductive organs suggests a role for the endocannabinoid system not only in reproduction (for which there is now substantial evidence; for a review see Gorzalka & Hill, 2006), but also potentially in sexual functioning. Specifically, whether acting on the hypothalamus or directly on the gonads, cannabinoids may affect the release of adrenal steroids implicated in sexual functioning. In support of this possibility, research has shown that THC administration increases levels of adrenocorticotropic hormone (ACTH) and corticosterone in rats (Jackson & Murphy, 1997; Manzanares, Corchero, & Funtes, 1999). ACTH is a hormone released by the pituitary in response to corticotropin releasing hormone, a hypothalamic hormone, which in turn leads to the release of glucocorticoids such as corticosterone from the adrenal cortex. Duplicating this effect with the endocannabinoid AEA, Wenger, Ledent, and Tramu (2003) found similar results in mice, and D'Souza and colleagues found that THC increased cortisol levels in humans (D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004). Given that THC and AEA increase ACTH, and ACTH leads to increased glucocorticoid release, it is likely that increased ACTH also leads to increased release of adrenal androgens including androstenedione (the major androgen produced by the adrenal cortex), and there is significant research evidence linking adrenal androgens and sexual function in women (e.g., Basson et al., 2010; Guay, Jacobson, Munarriz, Traish, Talakoub, Quirk, et al., 2004; Hackbert & Heiman, 2002; Hamilton & Meston, 2010; Motofei & Rowland, 2005; Spark, 2002). Further, Kolodny and colleagues found that women with lengthy histories of frequent cannabis use had significantly higher plasma testosterone levels (in addition to self-reports of more frequent sexual activity and orgasm) as compared to women with no history of cannabis use (Kolodny, Bauman, Biggs, Webster, &

Dornbush, 1977, as cited in Gorzalka & Hill, 2006; Kolodny et al., 1979); however, these latter results need to be interpreted with caution as they were not replicated in a subsequent study (Block, Farinpour, & Schlechte, 1991). It is possible that these conflicting results were due to differences in marijuana dose, frequency of use, and/or length of use across participants in the two studies, or to elevated baseline testeosterone levels that predated marijuana use in the women in the study by Kolodny et al. (1977); however, further research is needed to investigate these possibilities. Nevertheless, this accumulating evidence of the effects of cannabinoids on hormone release and the location of cannabinoid receptors throughout the brain and body continues to add to the research supporting the potential role of the endocannabinoid system in sexual functioning.

Effects of Cannabinoid Receptor Activation on Neurotransmitter Release

The final line of evidence supportive of a potential role for the endocannabinoid system in female sexual behaviour comes from the known effects of cannabinoid receptor activation on neurotransmitter release. As described above, the CB_1 receptor is a presynaptic receptor 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 (Bloom, 1982; Romero, Garcia, Cebeira, Zadrozny, Fernandez-Ruiz, & Ramos, 1995; Schlicker & Kathmann, 2001), 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 behaviours. In particular, increased serotonin and decreased dopamine have both been found to have deleterious effects on sexual functioning (e.g., Damsma, Pfaus, Wenksten, Phillips, & Fibiger, 1992; Melis

& Argiolas, 1995), as supported by the significant sexual side effects accompanying the use of serotonin re-uptake inhibitor antidepressants and dopamine-antagonistic antipsychotic medications (Compton & Miller, 2001; Meston & Gorzalka, 1992; Williams, Baldwin, Hogue, Fehnel, Hollis, & Edin, 2006). Both increased serotonin and decreased dopamine result in increased prolactin release, and increased prolactin has been associated with inhibited sexual functioning in men as well as women (e.g., Buvat, Lemaire, Buvat-Herbaut, Fourlinnie, Racadot, & Fossati, 1985; Koppelman, Parry, Hamilton, Alagna, & Loriaux, 1987). Increases in prolactin levels occur naturally following orgasm in both sexes, leading some to hypothesize that increased prolactin levels act as a feedback control on sexual drive, thereby facilitating the post-orgasmic refractory period (Kruger, Haake, Hartmann, Schedlowski, & Exton, 2002). Therefore, the chronic heightened prolactin levels accompanying the use of medications which either increase serotonin or decrease dopamine lead to a state of hyperprolactinemia, which in turn is implicated in significant decreases in sexual desire (Halbreich, Kinon, Gilmore, & Kahn, 2003). It is also noteworthy that a number of studies have found that acute administration of THC inhibits prolactin (as well as luteinizing hormone) secretion from the anterior pituitary in overiectomized female rats (e.g., Ayalon, Nir, Cordova, Bauminger, Puder, Naor, et al., 1977; Chakravarty, Sheth, & Ghosh, 1975; Dalterio, Mayfield, & Bartke, 1983), but increases prolactin secretion in estradiol-treated females (Scorticati, Fernandez-Solari, De Laurentiis, Mohn, Prestifilippo, Lasaga, et al., 2004; Scorticati, Mohn, De Laurentiis, Vissio, Fernandez-Solari, Seilicovich, et al., 2003), suggesting that endocannabinoids may regulate the hypothalamic-pituitary-gonadal (HPG) axis (López, 2010).

The Current Research

Altogether, then, these four lines of evidence from studies in humans and other species provide preliminary support for the hypothesis that the endocannabinoid system plays a role in female sexual functioning. 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 levels* in women, have been conducted, the role of the endocannabinoid system in human female sexual functioning remains unknown. Therefore, the present research was conducted to investigate this through studies using a physiological measure of sexual function as well as through measurement of endocannabinoid levels in relation to sexual function.

As previously discussed, past studies on this topic have, in part, been limited by the lack of clear definitions with respect to sexual function. Given that the human sexual response cycle is comprised of multiple stages (Masters & Johnson, 1966; Kaplan, 1979, Lief, 1977), and given that it is possible that the endocannabinoid system plays a different role at each stage, clear definitions of sexual outcomes are necessary in any research on this topic. The following line of research looked specifically at the relationship between the endocannabinoid system and one specific phase of the human sexual response—sexual *arousal*. Sexual arousal was divided into physiological sexual arousal (i.e., presence of the female genital lubrication swelling response) and subjective sexual arousal (i.e., presence of subjective excitement and pleasure, or feeling mentally 'turned on'), as proposed by Basson (2001, 2002a, 2002b). The relationship between the endocannabinoid system and these two forms of 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.

Specifically, the current research utilized vaginal photoplethysmography to measure physiological sexual arousal. The vaginal photoplethysmograph is a small, tampon-shaped device which is self-inserted into the vagina. The device is composed of an acrylic probe 1.5 cm in diameter and 4.5 cm in length that contains an infrared or incandescent light-emitting diode (LED) and a photosensitive light detector (photodiode). Genital engorgement has been found to occur within 20 seconds of exposure to visual and auditory sexual stimuli in sexually functional, premenopausal women (Meston, 2000), and involves increases in vaginal blood flow and consequent increases in vaginal lubrication. With respect to the vaginal photoplethysmograph, increased blood volume within the vaginal blood vessels during sexual arousal results in more backscattered light from the LED (Levin, 1992), which in turn is detected by the photodiode and transmitted to a filter, after which the signal is amplified and adjusted (Sintchak & Geer, 1975).

The vaginal photoplethysmograph is capable of measuring both vaginal blood volume (VBV) and vaginal pulse amplitude (VPA), which provide indirect indices of genital engorgement. VBV reflects the gradual pooling of blood within the vaginal wall. In contrast, VPA reflects phasic changes in vaginal engorgement with each heart beat that is dependent on changes in vaginal blood vessel pressure (Jennings, Tahmoush, & Redmont, 1980), with higher amplitudes indicative of greater genital engorgement (Geer, Morokoff, & Greenwood, 1974). The vaginal photoplethysmograph is a measure that has been demonstrated to be highly sensitive and specific to sexual stimuli (Hoon, Wincze, & Hoon, 1976), although VPA has been shown to be the more sensitive and valid measure of sexual arousal than VBV (Geer et al., 1974; Hieman,

1977; Laan, Everaerd, & Evers, 1995; Laan, Everaerd, van der Velde, & Geer, 1995). In addition, VPA is less vulnerable to movement artifacts (Laan et al., 1995), and has been found to be more closely associated with self-reported sexual arousal (Heiman, 1977), than VBV.

It should be noted that numerous other physiological measures of sexual arousal in women have been developed, including clitoral photoplethysmography (Gerritsen, van der Made, Bloemers, van Ham, Kleiverda, Everaerd, et al., 2009), laser Doppler imaging (Waxman & Pukall, 2009), clitoral Doppler ultrasonography (Kukkonen, Paterson, Binik, Amsel, Bouvier, & Khalife, 2006), clitoral electromyography (Yilmaz, Soylu, Ozcan, & Caliskan, 2002), and measures of labial temperature (Henson, Rubin, Henson, & Williams, 1977). However, vaginal photoplethysmography is not only the most widely used measure of physiological sexual arousal in women (Hatch, 1979), with established validity (Hoon et al., 1976), but it also has numerous benefits over other measures. For example, insertion of the vaginal photoplethysmograph does not require assistance by an experimenter or specialized technician. In contrast, clitoral Doppler ultrasonography and clitoral electromyography both require the assistance of the experimenter. This can not only deter potential participants from taking part in the research, but can also inhibit sexual arousal in women who do agree to participate in research utilizing these measures. Further, the ability of measures such as laser Doppler imaging and clitoral photoplethysmography to differentiate between sexually functional and dysfunctional women has not been established to date. In contrast, the vaginal photoplethysmograph has been shown to differentiate between sexually functional and dysfunctional women (e.g., Brotto, Klein, & Gorzalka, 2009; Palace & Gorzalka, 1992).

The current line of research involved three experiments. The first experiment was designed as a preliminary study to explore whether any relationships between serum endocannabinoid levels and sexual arousal (both physiological and subjective) in sexually healthy women existed. The second experiment expanded on the first by using more stringent inclusion and exclusion criteria, recruiting a larger sample of participants, using an additional technique designed to stimulate greater physiological sexual arousal in the laboratory, and adding a continuous measure of subjective sexual arousal to the protocol. The third experiment explored the relationship between marijuana use and both subjective and physiological measures of sexual arousal.

Specific hypotheses that were developed prior to initiating each experiment are described in the following chapters pertaining to each experiment; however, based on the literature previously reviewed of the self-reported effects of cannabis on human female sexual functioning, the observable effects of exogenous cannabinoids on sexual functioning in non-human animal species, the location of cannabinoid receptors throughout areas of the brain and periphery that are critical for sexual functioning, and the effects of cannabinoids on neurotransmitters implicated in sexual functioning, it was hypothesized that the following line of research would provide further support for the role of the endocannabinoid system in female sexual function by establishing a link between serum endocannabinoids and sexual arousal (both physiological and subjective), and by establishing a link between the use of exogenous cannabinoids and physiological sexual arousal.

Evidence that the endocannabinoid system plays an integral and direct role in female sexual functioning has significant implications not only for knowledge of female sexual

physiology—which to date has remained poorly understood—but also for the treatment of sexual dysfunctions. For example, if the endocannabinoid system plays a direct role in female sexual functioning, and female sexual dysfunctions (whether ideopathic or iatrogenic) are found to be associated with either over-activation or under-activation of this system, pharmacological treatments designed to activate or suppress this system have the potential to be of significant benefit. Further, understanding the potential role of this system in sexual functioning allows for the anticipation of possible sexual side effects of pharmacological treatments currently being developed for various nonsexual disorders that exert their effects by facilitating or antagonizing the endocannabinoid system (e.g., rimonabant, taranabant; Gorzalka et al., 2010).

Experiment 1: Endocannabinoids and Female Sexual Arousal Preliminary Study

As previously reviewed, multiple lines of converging evidence are accumulating, suggesting that the endocannabinoid system serves a role in female sexual functioning. These lines of evidence include results from studies of the self-reported effects of cannabis consumption on sexual functioning in women (Dawley et al., 1979; Goode, 1969; Halikas et al., 1982; Johnson et al., 2004; Koff, 1974; Kolodny et al., 1979; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970), the observable effects of exogenous cannabinoid agonists and antagonists on the sexual behaviours of non-human animal species (Ferrari et al., 2000; Gordon et al., 1978; López et al., 2009, 2010; Mani et al., 2001; Turley & Floody, 1981), the location of cannabinoid receptors throughout areas of the brain and periphery critical for sexual functioning (Geliegue et al., 1995; Herkenham et al., 1991; Rodriguez de Fonseca et al., 1994; Tsou et al., 1998), and the effects of cannabinoid receptor activation on the release of neurotransmitters implicated in sexual functioning (Bloom, 1982; Romero et al., 1995; Schlicker & Kathmann, 2001).

With respect to research conducted in human females, data collection has been restricted to studies utilizing self-reports. Self-report measures are important, particularly when assessing sexual function; however, multiple factors can affect the validity of self-reports, limiting the conclusions that can be drawn from this source of data. For example, self-reports are susceptible to exaggeration or to minimization, to forgetting when self-reports depend on retrospective recall, and to various biases such as the social desirability bias and demand characteristics (for a review, see Podsakoff, MacKenzie, Lee, & Podsakoff, 2003).

In addition, none of the self-report measures used in past studies on the relationship between cannabis consumption and sexual function were validated measures. Rather, each study developed its own set of questions, many of which failed to define sexual constructs or were ambiguous with respect to the specific phase(s) of the human sexual response being queried. This has made it impossible to accurately interpret the results of studies, or to summarize across studies, other than to summarize that cannabis use has been consistently associated with sexual effects in women and, with one exception (Johnson et al., 2004), these effects were perceived by respondents to be facilitatory.

Further complicating any conclusions about the role of the endocannabinoid system in sexual function is that past studies have been correlational in nature and, as previously reviewed, numerous plausible possibilities exist for cannabis consumption to enhance subjective perceptions of sexual functioning without exerting any direct effects on sexual response. These include the possibilities that cannabis may increase sensation or perception (Abel, 1981; Dawley et al., 1979; Halikas et al., 1982), decrease anxiety/facilitate relaxation (Adams & Martin, 1996; Hathaway, 2003; Kolodny et al., 1979), slow the perception of time and increase attentional focus on the sexual situation (Gawin, 1978; Jarvik & Brecher, 1977; Lewis, 1970; Melges et al., 1971), reduce inhibitions (Dawley et al., 1979; Kolansky & Moore, 1972; Kolodny et al., 1979; McKay, 2005), or lead to perceptions of enhanced sexual functioning through expectancy effects (Crenshaw & Goldberg, 1996; Rosen, 1991).

As a result of these limitations, studies are needed that use validated measures to assess not only subjective, but also physiological, sexual response, and that define the specific phase(s) of the human sexual response being measured. Further, human experimental studies, in which the

effects of cannabinoid agonists and/or antagonists on sexual behaviour are systematically measured, are needed in order to definitively discern the role, if any, of the endocannabinoid system in human female sexual functioning. However, due to ethical restrictions on conducting research of this nature, it is understandable why this research has not been performed to date.

The following line of research was designed and conducted in an attempt to investigate the relationship between the endocannabinoid system and sexual function in human females. Experiment 1 was designed as a small preliminary study in order to conduct an initial investigation of whether the endocannabinoid system is directly related to sexual response in women. Specifically, the objective of this preliminary study was to investigate whether changes in physiological and subjective sexual arousal (elicited by erotic film stimuli and measured via validated instruments) are accompanied by changes in serum endocannabinoid levels (AEA and 2-AG), and, if found to be the case, to assess the direction of these changes (i.e., whether endocannabinoid levels increase or decrease in relation to increased sexual arousal).

Based on the previously summarized research of both the subjective effects of cannabis consumption on sexual function in humans and the observable effects of cannabinoid agonists and antagonists on the sexual behaviours of non-human animal species, it was hypothesized that there would be a correlation between endocannabinoid levels 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) levels. This latter hypothesis was based on the fact that past studies in women have, with only one exception, found cannabis to be related to enhanced perceptions of sexual function, suggesting that elevated cannabinoid levels are associated with heightened sexual response. As a result, it was

hypothesized that elevated sexual arousal in the current study would similarly be associated with elevated levels of endocannabinoids.

Endocannabinoids cross the blood-brain barrier (Mechoulam, Fride, & Di Marzo, 1998; Willoughby, Moore, Martin, & Ellis, 1997); thus, circulating levels may indirectly reflect brain levels. A finding of altered endocannabinoid levels in relation to changes in physiological and/or subjective measurements of sexual arousal would provide preliminary evidence that endocannabinoids are directly related to sexual arousal in women, and would provide the impetus for further research in this area, including the potential role of the endocannabinoid system in the onset, maintenance, and treatment of sexual arousal difficulties. This is the first study to date to examine serum endocannabinoid levels in relation to sexual function and, more specifically, in relation to sexual arousal, in women.

Method

Participants

Participants were 10 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 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. Further exclusion criteria included the use of any illicit substances (including cannabis) in the last month, current or past pregnancy over the last year, 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.

Apparatus and Materials

Film Stimuli. Film stimuli consisted of two, 14-minute, films which included a 1-minute display of the word "relax" followed by a 3-minute 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-minute 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 (Basson & Brotto, 2003; Brotto et al., 2009). The different segments of the films were professionally spliced together to form one continuous videotape with audio accompaniment.

Vaginal Photoplethysmograph. Vaginal photoplethysmography (Sintchak & Geer, 1975) was used to measure physiological sexual arousal. As previously described, the vaginal photoplethysmograph is a small, tampon-shaped device which is self-inserted into the vagina. The device measures vaginal vasocongestion, which is an indirect measure of 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 (Geer, Morokoff, & Greenwood, 1974; Heiman, 1977; Laan et al., 1995). VPA reflects phasic changes in vaginal engorgement with each heart beat, such that higher amplitudes indicate greater genital engorgement (Geer et al., 1974). The vaginal photoplethysmograph is the most validated and most commonly used physiological instrument to measure sexual arousal in women (Woodward & Diamond, 2009).

The photoplethysmograph was turned on 30 minutes prior to use in order to minimize potential light history and temperature sensitivity effects. After the photoplethysmograph had been inserted, a 5-minute 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 (e.g., Brotto, Basson, & Gorzalka, 2004; Brotto & Gorzalka, 2002; Brotto et al., 2009), data were analyzed in 30-second 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. The photoplethysmograph was sterilized in Cidex (long-life activated dialdehyde solution) between uses.

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 (1983) 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 (Heiman, 1980; Heiman & Rowland, 1983; Heiman & Hatch, 1980).

Antecubital Venipuncture. Antecubital venipuncture to measure serum endocannabinoid levels 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 one hour following venipuncture. Samples were subsequently centrifuged for 15 minutes at 1000 x 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 [2H8]-AEA (16.9 pmol) and [2H8]-2-AG (46.5 pmol) (Cayman Chemicals, Ann Arbor, MI). Samples were vortexed and centrifuged at 1000 x g for four minutes. The supernatant was loaded on C18 columns conditioned with 1 ml redistilled ethanol and 3 ml of distilled water. The remaining pellet was washed with 100 µL of 15% ethanol and again centrifuged for 3 minutes. Resulting supernatant was then 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 subsequently removed and dried under N_2. Lipids in the residual double distilled water phase were extracted by mixing with an additional 1 ml of ethyl acetate added to the original ethyl acetate solution. 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 in Patel, Carrier, Ho,

Rademacher, Cunningham, Reddy, et al. (2005), and is identical to that used in previous research involving the measurement of AEA and 2-AG in human serum (e.g., Hill, Miller, Carrier, Gorzalka, & Hillard, 2009; Hill, Miller, Ho, Gorzalka, & Hillard, 2008).

Procedure

All participants were recruited through advertisements posted throughout the campus of the University of British Columbia. 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 honourarium in exchange for study participation would be provided. Women interested in participating were asked to call the UBC Sexual Psychophysiology and Neuroendocrinology 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 relating to their medical history as well as past and current drug use (including both prescription and illicit drugs) 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. Both sessions involved the measurement of serum endocannabinoid levels before and after the presentation of either neutral film stimuli (control session) or erotic film stimuli designed to elicit sexual arousal (experimental session). All participants had both sessions scheduled in the mornings to avoid confounding of endocannabinoid levels with diurnal hormone variations, and the sessions were counterbalanced across participants. Both sessions were held in

the UBC Sexual Psychophysiology and Neuroendocrinology Laboratory, located in the Department of Psychology on the campus of the University of British Columbia.

At the beginning of the first session, participants were shown the laboratory and the equipment used to measure sexual arousal and collect serum. The study purpose was re-explained, participants were given the opportunity to ask questions, and written informed consent was obtained.

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 privacy. Participants remained clothed and were able to cover themselves with a blanket at all times.

Once the photoplethysmograph was comfortably inserted, participants notified the experimenter by speaking through a voice-activated intercom between the participant and experimenter rooms. 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 via a 21-gauge, ¾-inch butterfly needle attached to a serum separating tube.

Immediately after the first venipuncture, the experimenter once again left the room and participants were instructed to complete the 1-page subjective measure of arousal questionnaire asking about their current subjective ratings of sexual arousal, autonomic arousal, anxiety, and positive and negative affect. As soon as participants completed the questionnaire, they 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. As previously described, videos began with the word "relax" presented on the screen for one minute, followed by 3 minutes of neutral footage (in order to establish a baseline), followed by 10 minutes of either additional neutral footage (the control session) or erotic footage (the experimental session). During presentation of the films, physiological sexual arousal was measured via the vaginal photoplethysmograph. This protocol for eliciting and measuring physiological sexual arousal has been used repeatedly in previous research in our laboratory (e.g., Brotto, Gehring, Klein, Gorzalka, Thomson, & Knudson, 2005; Brotto & Gorzalka, 2002; Brotto et al., 2009; Meston & Gorzalka, 1996; Palace & Gorzalka, 1990).

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 questionnaire; 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. At this time, participants were again given the opportunity to ask any questions and the second session was scheduled.

The second session was scheduled approximately one week after the first. This 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 honourarium.

Data Analysis

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) levels 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 levels 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 levels

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 .05 was deemed statistically significant.

Results

Effects of Film Stimuli on Physiological and Subjective Sexual Arousal

A significant difference was found between physiological sexual arousal in the control as compared to the erotic condition [$t(9) = 3.77$, $p = .004$], with physiological sexual arousal being significantly greater in response to the erotic (experimental) film than in response to the neutral (control) film.

With respect to the three indices of subjective sexual arousal (i.e., mental sexual arousal, subjective physiological 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 [$F(3,7) = 25.41$, $p < .001$]. Follow-up univariate tests revealed significant differences for all three indices—subjective physiological sexual arousal [$t(9) = 4.94$, $p = .001$], mental sexual arousal [$t(9) = 3.87$, $p = .004$], and overall subjective sexual arousal [$t(9) = 8.14$, $p < .001$]—with the experimental condition again leading to increased sexual arousal compared to the control condition.

Effects of Film Stimuli on Endocannabinoid Levels

Changes in endocannabinoid (AEA and 2-AG) levels from pre-film to post-film in the experimental and control conditions are presented in Table 1, separately for all ten participants, along with changes in physiological sexual arousal and changes in the three indices of subjective sexual arousal. No significant changes in either AEA or 2-AG levels were found in either the

experimental or the control condition (all *p*'s > .20)—a finding that was not surprising given that, as can be seen in Table 1, there was significant variability in the direction and magnitude of change in both AEA and 2-AG levels. For example, 2-AG levels in participant no. 4 showed an *increase* of 7.12 pmol/mL in the experimental condition, while 2-AG levels in participant no. 9 showed a *decrease* of 6.07 pmol/mL in the same condition. In contrast to these differences, participant no. 1 showed almost no change.

Table 1

Changes in Endocannabinoid Levels, Physiological, and Subjective Sexual Arousal during the Experimental and Control Films

	EXPERIMENTAL						CONTROL					
P	AEA	2-AG	VPA	PHYS	MEN	OVER	AEA	2-AG	VPA	PHYS	MEN	OVER
1	-0.09	0.71	34.76	18	20	5	-0.93	-0.54	-14.83	0	-2	0
2	-2.84	-3.57	14.33	8	-6	2	-1.15	-0.78	0.61	2	-3	-1
3	-0.32	1.97	83.83	8	9	3	3.02	7.97	-4.13	-2	-1	-1
4	1.77	7.12	89.94	14	8	4	-0.45	1.79	0.20	-1	-3	-1
5	0.18	-1.90	-15.71	8	5	3	-0.82	-2.36	-12.08	-4	-1	-1
6	0.62	-3.34	140.73	5	6	2	0.04	3.57	-4.58	0	0	0
7	-0.70	5.73	54.54	4	9	1	0.28	5.86	4.11	-2	-1	-1
8	0.22	-2.81	188.63	22	27	6	-2.29	1.90	-1.23	-6	-2	0
9	-2.08	-6.07	16.06	7	-3	2	-0.41	-3.31	1.42	1	-9	0
10	-0.02	-0.57	142.31	22	12	5	0.35	0.11	-16.10	-4	-4	0

Note. EXPERIMENTAL = experimental condition; CONTROL = control condition; P = participant number; AEA = change in arachidonoylethanolamide from pre- to post-film in pmol/mL; 2-AG = change in 2-arachidonoylglycerol from pre- to post-film in pmol/mL; VPA = vaginal pulse amplitude % change over course of film; PHYS = subjective physiological sexual arousal difference score from pre-film to post-film (possible range = -30 – +30); MEN = mental sexual arousal difference score from pre-film to post-film (possible range = -36 – +36); OVER = overall subjective sexual arousal difference score from pre-film to post-film (possible range = -6 – +6).

Relationship Between Endocannabinoids and Sexual Arousal

Descriptive statistics (means and standard deviations) and Pearson product moment correlations between endocannabinoid levels, physiological sexual arousal, and indices of subjective sexual arousal are presented in Table 2. As shown in Table 2, no significant correlations were found between the two types of endocannabinoids or between endocannabinoid levels and either physiological sexual arousal or subjective sexual arousal in the experimental condition (all *p*'s > .09). In contrast, a significant positive correlation between AEA and 2-AG was found in the control condition ($r = .65$, $p = .043$), although no significant correlations were found between endocannabinoids and either physiological or subjective indices of sexual arousal in the control condition (all *p*'s > .06).

Relationships Between Indices of Sexual Arousal

As can be seen in Table 2, in the experimental condition, no significant correlations were found between physiological sexual arousal and either subjective physiological sexual arousal or overall subjective sexual arousal (both *p*'s > .10), although a marginally significant correlation was found between physiological sexual arousal and mental sexual arousal ($r = .63$, $p = .051$). Significant correlations were found between the three indices of subjective sexual arousal ($r = .72$, $p = .019$ for the correlation between subjective physiological sexual arousal and mental sexual arousal; $r = .96$, $p < .001$ for the correlation between subjective physiological sexual arousal and overall subjective sexual arousal, and $r = .78$, $p = .008$ for the correlation between mental sexual arousal and overall subjective sexual arousal).

In the control condition, no significant correlations were found between any of the indices of sexual arousal, whether between physiological and subjective indices, or whether between the subjective indices, themselves (all *p*'s > .30).

Relationships Between Endocannabinoids, Autonomic Arousal, and Affect

Changes in AEA and 2-AG levels were not significantly correlated with changes in autonomic arousal, anxiety, positive affect, or negative affect from pre-film to post-film in either the experimental or the control condition (all *p*'s > .08).

Table 2

Means, Standard Deviations, and Correlations for the Relationships Between Endocannabinoids and Physiological and Subjective Sexual Arousal

EXPERIMENTAL CONDITION

Variables	2-AG	VPA	PHYS	MEN	OVER	*M*	*SD*
AEA	.54	.49	.34	.56	.46	-0.33	1.31
2-AG	__	.06	.02	.25	.02	-0.27	4.21
VPA	__	__	.53	.63^	.52	74.94	66.24
PHYS	__	__	__	.72*	.96*	11.60	6.87
MEN	__	__	__	__	.78*	8.60	9.75
OVER	__	__	__	__	__	3.30	1.64

CONTROL CONDITION

Variables	2-AG	VPA	PHYS	MEN	OVER	*M*	*SD*
AEA	.65*	-.03	.10	.16	-.31	-0.24	1.38
2-AG	__	.30	-.17	.60	-.32	1.42	3.57
VPA	__	__	.30	-.17	-.35	-4.66	7.20
PHYS	__	__	__	-.31	-.08	-1.60	2.50
MEN	__	__	__	__	-.33	-2.60	2.55
OVER	__	__	__	__	__	-0.50	0.53

Note. EXPERIMENTAL = experimental condition; CONTROL = control condition; AEA = arachidonoylethanolamide; 2-AG = 2-arachidonoylglycerol; VPA = vaginal pulse amplitude; PHYS = subjective physiological sexual arousal; MEN = mental sexual arousal; OVER = overall subjective sexual arousal.

*$p < .05$

^$p < .06$

Discussion

As expected, based on past research utilizing the same film stimuli as were used in the current study (e.g., Brotto et al., 2005; Brotto, Klein, & Gorzalka, 2009), the erotic (experimental) film resulted in significantly enhanced physiological and subjective sexual arousal as compared to the neutral (control) film. This provides evidence that the experimental film manipulation was effective in eliciting sexual arousal in participants, although as can be seen in Table 1, participant no. 5 showed a decrease in physiological sexual arousal during the erotic film. This, however, is not uncommon in the literature on physiological sexual arousal in women, where up to 30% of women do not become physiologically aroused in response to erotic film stimuli (Rellini, McCall, Randall, & Meston, 2005), as evidenced by either a decrease or a lack of a significant increase in physiological sexual arousal (e.g., Henson, Rubin, & Henson, 1979).

Similarly, two participants in the experimental condition reported decreases in one index of subjective sexual arousal (mental sexual arousal) over the course of the erotic film. This finding is also not, altogether, surprising, given that some women have given feedback following participation in our research studies reporting that they entered the studies feeling mentally sexually excited in anticipation of viewing erotic film stimuli, only to subsequently find that the erotic film stimuli were not as mentally arousing as initially anticipated and/or that the artificial laboratory setting made it difficult to maintain mental sexual arousal over the course of the film. Nonetheless, the fact that nine out of ten participants showed an increase in physiological sexual arousal, and that this increase was statistically significant, and, similarly, that significant

increases in all three indices of subjective sexual arousal were seen in the experimental condition attests to the validity of the film manipulation used in this study.

The results from this preliminary study were surprising, however, in that no significant changes in AEA or 2-AG levels were seen over the course of the experimental film and that, as would then be expected, no significant correlations between either AEA or 2-AG and sexual arousal (both physiological and subjective) were found. These findings are contrary to our original hypotheses and bring into question whether the endocannabinoid system is associated with sexual arousal in women.

The lack of significant effects in this preliminary study may, however, be due to any of a number of factors relating to sample size and study methodology. With respect to sample size, this study was designed to be a preliminary study and, thus, was composed of only a small number of women. With a sample size of only 10 women, it is quite conceivable that any meaningful associations were masked by uncontrolled variables affecting either endocannabinoid levels and/or sexual arousal in a few or even all of the participants.

With respect to study methodology, because this study was designed to be a preliminary study, numerous methodological short-cuts were taken which, in retrospect, may have compromised the findings. Specifically, although all sessions in this study were scheduled in the mornings to control for the effects of diurnal hormone variations on endocannabinoid levels and/or sexual arousal, other factors capable of affecting endocannabinoid levels were not controlled. For example, as the endocannabinoid system plays a critical role in appetite and food regulation (Cota et al., 2003; Di Marzo & Matias, 2005), and endocannabinoid levels rise during fasting and drop with satiation (Kirkham, Williams, Fezza, & Di Marzo, 2002), any food

ingested prior to study participation would have altered endocannabinoid levels. As a result, if some participants attended the session on an empty stomach, their baseline endocannabinoid levels may have been considerably higher than those of participants attending the session following caloric intake. This may have resulted in ceiling and floor effects, respectively, across participants, thereby obscuring any effects of sexual arousal on endocannabinoid levels. As such, an important methodological limitation of this study may have been that participants were not required to either uniformly fast or uniformly eat prior to study participation. Similarly, level of stress prior to participation may have influenced endocannabinoid levels, as the endocannabinoid system is implicated in homeostasis and the stress response (Gorzalka et al., 2008; Hill, et al., 2009).

A second factor which was not controlled for in this pilot study, but which may have affected endocannabinoid levels, was phase of the menstrual cycle. All participants were scheduled to take part in the second session approximately one week after the first session. However, a more rigorous design controlling for phase of the menstrual cycle by scheduling sessions either one day or 28 days apart, rather than 7 days apart, would have prevented the potential confound of menstrual cycle-related hormone variations.

Thirdly, while participants were screened for acute and chronic medical conditions, specific and detailed screening for sexual difficulties was not conducted. As it is hypothesized that the endocannabinoid system plays a role in female sexual functioning, it follows that in women experiencing a sexual dysfunction, endocannabinoid levels may be affected and may not respond in a "normal" way to erotic stimuli. Further, past research indicates that women with sexual difficulties respond differentially to erotic stimuli than do women with no sexual

difficulties (Meston & Gorzalka, 1996). Thus, if any of the women in the current sample were experiencing sexual difficulties but did not disclose them to the study experimenter because sexual difficulties were not specifically queried under the exclusion criteria, both endocannabinoid and sexual arousal outcome measures may have been affected.

Finally, the possibility that sexual arousal levels attained in this study were insufficient to significantly alter endocannabinoid levels cannot be ruled out. As sexual arousal induced in the laboratory setting is unlikely to produce the levels of arousal attained in naturalistic settings, the current protocol for enhancing sexual arousal may have been insufficient to produce noticeable changes in endocannabinoid levels, particularly if endocannabinoids play a role in female sexual arousal only at higher levels of arousal.

With respect to the relationships found between the various indices of sexual arousal, this study found significant correlations between subjective indices of sexual arousal, but not between physiological and subjective indices (although a marginally significant correlation was found between physiological sexual arousal and mental sexual arousal). This "desynchrony", or lack of concordance, between physiological and subjective measures is common in the literature on sexual arousal in women (e.g., Geer et al., 1974; Brotto et al., 2009; Laan & Everaerd, 1995; Laan, Everaerd, van Bellen, & Hanewald, 1994; Laan et al., 1995; Morokoff & Heiman, 1980; Meston & Gorzalka, 1995; Palace & Gorzalka, 1990; 1992; Rosen & Beck, 1988; Steinman, Wincze, Sakheim, Barlow, & Mavissakalian, 1981; Wincze, Hoon, & Hoon, 1976; see also Chivers, Seto, Lalumière, Laan, & Grimbos, 2010).

Numerous explanatory hypotheses have been put forth for findings of low or no concordance. For example, Palace and Gorzalka (1990) hypothesized that women may not

express subjective sexual arousal as a result of social dictates that discourage women from attending to, or acknowledging, their arousal. Heiman (1976, 1977) postulated that, in contrast to men, women lack an obvious bodily cue (i.e., erection) to give them feedback about their physiological arousal, which can result in discordance between physiological and subjective sexual arousal. Chivers and Bailey (2005) proposed that physiological and subjective sexual arousal are two separate components of overall sexual arousal. Specifically, based on research in which they found that women—but not men—show a physiological sexual arousal response to sexual stimuli involving non-human primates (while denying any subjective sexual arousal), they proposed that women's genital vasocongestion is provoked by exposure to nonspecific sexual features, independent of what those features are. Further, they proposed that this response may be an evolved adaptation which protects women from physical harm or infection by preparing the vagina for sexual activity. In essence, according to this hypothesis, women become physiologically aroused in the presence of non-specific sexual stimuli but then make a cognitive appraisal of the stimuli as either subjectively arousing or not. In contrast, Rellini et al. suggested that the apparent lack of concordance seen in women may be due to methodological and statistical issues which mask the actual concordance between the two indices (Rellini et al., 2005).

Overall, then, the current study failed to provide evidence of a relationship between the endocannabinoid system and female sexual arousal. It should, however, be noted that the current study was designed to investigate changes in endocannabinoid levels only in response to changes in sexual *arousal*, but that the endocannabinoid system may play a role in any aspect of sexual functioning, from desire, to arousal, to orgasmic functioning. Thus, even if the current findings

of no relationship between endocannabinoids and female sexual arousal are representative of the true relationship between these variables, these findings do not exclude the potential role of the endocannabinoid system in female sexual desire and orgasmic functioning.

Ultimately, due to the numerous methodological and sample size limitations discussed, the results from the current study shed little light on the question of the role of the endocannabinoid system in female sexual functioning. Research involving far more stringent and well-controlled methodology and a larger sample size are needed.

Experiment 2: Revised Study on the Relationship between Endocannabinoids and Female Sexual Arousal

Experiment 1 failed to reveal any significant relationships between endocannabinoid levels and sexual arousal in women. This may reflect that there are no direct relationships between the endocannabinoid system and sexual arousal in women or, as previously discussed, that any relationships were obscured by sample size and methodological limitations. These methodological limitations included the fact that the design of Experiment 1 did not control for factors known to have an impact on endocannabinoid levels such as food intake, stress, and phase of the menstrual cycle, that participants were not specifically screened for sexual difficulties, and that sexual arousal levels elicited in the study may have been insufficient to evoke measurable changes in endocannabinoids.

Given, however, the rather extensive literature in humans and other species suggestive of a direct relationship between the endocannabinoid system and sexual functioning in women, and given that there were significant sample size and methodological limitations in the previous experiment which may have obscured this relationship, the present experiment was designed with the objective of reconciling the previous equivocal results through the collection of new data using revised study methods and a larger sample size. Specifically, this revised experiment 1) employed a sample size twice that of the preliminary study; 2) controlled for variables that can alter endocannabinoid levels, such as food intake, stress, and phase of the menstrual cycle; 3) specifically screened for the presence of any sexual difficulties; and 4) employed enhanced physiological sexual arousal, as sexual arousal induced in the laboratory setting via the

presentation of erotic film stimuli is unlikely to produce the levels of arousal attained in naturalistic settings.

With respect to the last point, the specific technique employed to enhance sexual arousal was laboratory-induced hyperventilation (LIH). LIH is a procedure which has been found to reliably increase sympathetic nervous system (SNS) activity and, thus, physiological sexual arousal (Brotto & Gorzalka, 2002; Brotto et al., 2009). 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 (Meston, Gorzalka, & Wright, 1997). Similarly, sexual arousal enhanced via increased SNS activity has been found to discriminate women with various sexual difficulties (Meston & Gorzalka, 1996)—findings which are again not apparent in the absence of increased SNS activity. Further, SNS activity naturally increases as sexual arousal increases (Wiedeking, Ziegler, & Lake, 1979), and as both SNS activity and endocannabinoids have a link to noradrenergic activity (Oropeza, Mackie, & Van Bockstaele, 2007), it is possible that if a relationship exists between the endocannabinoid system and sexual arousal, that it is mediated by noradrenergic activation. Therefore, a relationship between endocannabinoid levels and sexual arousal may only become apparent under conditions involving increased noradrenergic activity.

The present experiment had an additional aim. This aim pertained to the lack of concordance seen in Experiment 1 between physiological and subjective measures of sexual arousal. This lack of concordance, as previously noted, has been found repeatedly in past research (e.g., Geer et al., 1974; Brotto et al., 2009; Laan & Everaerd, 1995; Laan et al., 1994,

1995; Morokoff & Heiman, 1980; Meston & Gorzalka, 1995; Palace & Gorzalka, 1990; 1992; Rosen & Beck, 1988; Steinman et al., 1981; Wincze et al., 1976) and, thus, was not a surprising finding in Experiment 1; however, Rellini and colleagues have suggested and tested an important hypothesis for why this lack of concordance has been reported in women (Rellini et al., 2005). As a result, a secondary aim of Experiment 2 was independently to test their hypothesis.

Specifically, Rellini and her colleagues (2005) hypothesized that measuring subjective sexual arousal continuously and simultaneously with physiological sexual arousal (rather than non-continuously before and after the presentation of erotic stimuli), and then analyzing the data via hierarchical linear modeling (HLM), may lead to findings of significant concordance, rather than discordance, between these two measures of sexual arousal. In other words, Rellini's research team hypothesized that subjective and physiological sexual arousal are not, in fact, two distinct entities, but rather that methodological and statistical shortcomings have resulted in past findings of no or low concordance.

In particular, Rellini's team (2005) noted that non-continuous measures of subjective sexual arousal can be problematic when examining the concordance between subjective and physiological sexual arousal because non-continuous measures not only rely on retrospective recall, but also because non-continuous measures provide only limited information by collecting data at only two time points (pre and post) as opposed to collecting continuous measurements over the course of the erotic stimuli. Further, Rellini's group suggested that the typical methods used to analyze the concordance between physiological and subjective sexual arousal, in which physiological and subjective sexual arousal are reduced to one data point each, and then correlated, may also have contributed to past findings of low or no concordance in women.

Specifically, as pointed out by Rellini et al. (2005), "this methodology significantly reduces the richness of the data and does not allow for an assessment of how changes in one measure may be associated to changes in the other measure," (p. 117). Rellini et al. (2005) also noted that typical statistical methods of analyzing the relationship between subjective and physiological sexual arousal may have failed to detect concordance between these two measures since most sexual psychophysiological research studies have small sample sizes—something which is not problematic when looking at physiological measures with low error variance, but something which can become problematic when Likert-scale questionnaire data are used, which reduce statistical power and, thus, increase the potential for Type II errors.

Instead, Rellini and colleagues (2005) recommended that HLM be used, in part, because 1) HLM conducts a within-subjects analysis of the relationship between subjective and physiological sexual arousal and uses the coefficients from that relationship (i.e., slope and intercept) to test differences between participants; 2) HLM analyzes the within-subjects relationship, meaning that individual differences across participants in VPA do not pose a problem since the only between-subjects comparison is based on the strength of the within-subjects relationship; 3) HLM does not require the assumption of independence of observations; and 4) HLM has lower Type I error rates.

Rellini and her colleagues (2005) tested their hypothesis with a sample of 22 medically healthy women who did not have any sexual difficulties. When analyzing their results the "traditional" way, using Pearson's correlations, they found no significant association between physiological sexual arousal (i.e., VPA) and non-continuous subjective sexual arousal (i.e., sexual arousal measured via pre- and post-questionnaires). These results are identical to those

found in Experiment 1 of the present research. In line with their hypotheses, however, Rellini et al. found significant concordance between continuously measured physiological and subjective sexual arousal when analyzed via HLM, with VPA significantly predicting continuous subjective sexual arousal, and vice versa, for the overall sample. Based on these findings, Rellini et al. (2005) concluded that physiological and subjective sexual arousal are, in fact, related in women, and that past studies that failed to find this relationship were hampered by a reliance on non-continuous measures of subjective sexual arousal and by a reliance on statistical methods that are less sensitive to individual differences.

Thus, the objectives of Experiment 2 were not only to re-assess the relationship between endocannabinoids and sexual arousal in women via renewed data collection with a larger sample and a revised methodology, but also independently to test/replicate the hypotheses and findings of Rellini et al. (2005) with respect to the relationship between physiological and subjective sexual arousal. As previously discussed, the finding of a relationship between endocannabinoids and sexual arousal has potential significance in terms of gaining a better understanding of the physiology underlying sexual function in women and the development of potential pharmacological interventions for female sexual dysfunctions.

Discerning whether subjective and physiological sexual arousal are two distinct constructs in women, or whether past methodological and statistical methods have hampered detecting a concordance between measures of the same underlying construct, also has significant implications for the field of female sexuality. Specifically, due to the multitude of past studies which have failed to find significant relationships between subjective and physiological measures of sexual arousal in women (e.g., Geer et al., 1974; Brotto et al., 2009; Laan &

Everaerd, 1995; Laan et al., 1994, 1995; Morokoff & Heiman, 1980; Meston & Gorzalka, 1995; Palace & Gorzalka, 1990; 1992; Rosen & Beck, 1988; Steinman et al., 1981; Wincze et al., 1976), experts in the field of female sexual function have proposed that female sexual arousal disorder (FSAD) be re-classified, from its current classification as a disorder focused solely on physiological arousal impairments, to a delineation of three distinct subtypes (Basson, 2001, 2002a; Basson, Berman, Burnett, Derogatis, Ferguson, Fourcroy, et al., 2000; Basson, Leiblum, Brotto, Derogatis, Fourcroy, Fugl-Meyer, et al., 2003; 2004). These subtypes are: 1) genital FSAD, corresponding to the current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text-Revised (DSM-IV-TR, American Psychiatric Association [APA], 2000) and International Classification of Diseases, 10th Edition (ICD-10, World Health Organization, 1999) definitions of FSAD, in which there is absent or impaired physiological sexual arousal (i.e., minimal genital lubrication or swelling); 2) subjective FSAD, in which there is an absence or marked decrease in subjective feelings of sexual excitement and pleasure in response to sexual stimulation but genital lubrication and swelling remain intact; and 3) combined FSAD, in which both subjective *and* physiological sexual arousal are impaired.

If, however, physiological and subjective sexual arousal are both reflective of the same, underlying construct, this proposed delineation into separate subtypes of FSAD would no longer prove necessary or useful. Thus, this research has important implications for not only the development of a greater understanding of female sexual functioning, but also for the classification of female sexual dysfunctions. This seems particularly relevant now, as the DSM is preparing its fifth edition to be published in 2013 and the ICD is preparing its 11th edition, to be published in 2014.

Method

Participants

Twenty-one medically healthy premenopausal women between the ages of 19–45 were recruited to participate in this experiment. “Medically healthy,” as in Experiment 1, was defined as being in good self-reported physical health with no history of chronic medical illnesses and no indications of current acute infections; however, the definition for this revised pilot study also included detailed screening for the specific presence of any sexual difficulties as well as the presence of any mental health issues.

In addition to the exclusion criteria stipulated in Experiment 1, this study involved additional exclusion criteria. These consisted of a history of hormonal disorders including diabetes, as these disorders have been known to affect sexual functioning, and current breastfeeding of a child, as lactation is associated with altered hormone levels. Interested participants were also queried for a history of panic attacks as the LIH protocol can lead to physical sensations similar to those experienced during a panic attack. Women with a history of panic attacks were, therefore, asked about their comfort level in doing this type of exercise prior to participation.

Participant characteristics are presented in Table 3.

Table 3
Experiment 2 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)

Apparatus and Materials

The film stimuli, vaginal photoplethysmography system, non-continuous subjective measurement of arousal Likert scales, and antecubital venipuncture materials were identical to those used and described previously in Experiment 1. In addition, the following apparatus and materials were included in the present study:

Testing Conditions Interview. In order to control for factors that can affect endocannabinoid levels, 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 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; Derogatis, 1978; Derogatis & Melisaratos, 1979) 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. The other subtests assess 1) knowledge of sexual physiology, anatomy, and sexual function; 2) range of sexual experiences; 3) sexual drive; 4) sexual attitudes; 5) affects; 6) gender role definitions; 7) sexual fantasies; 8) body image; and 9) sexual satisfaction. 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. Higher scores on the DSFI indicate increased (better) sexual functioning. With respect to psychometric properties, Derogatis & Melisaratos (1979) found internal consistency reliability coefficients of between .60 and .97. Test-retest coefficients across a 14-day interval were found to be between the high .70s and the low .90s. These latter findings were supported by

Howell, Reynolds, Thase, Frank, Jennings, Houck, et al. (1987). With respect to discriminant validity, the DSFI has been shown to be a valid measure for differentiating sexually functional and dysfunctional women (e.g., Derogatis & Melisaratos, 1979; Derogatis & Meyer, 1979).

Female Sexual Function Index. The Female Sexual Function Index (FSFI; Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, et al., 2000) 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, higher scores on this measure indicate higher levels of sexual functioning. Also similar to the DSFI, the FSFI has been shown to be a valid measure for differentiating sexually functional and dysfunctional women (Rosen et al., 2000). The measure has a high degree of internal consistency (Cronbach's alpha $\geq .82$) and high test-retest reliability (test-retest reliability coefficiencts ranged from $r = .79$ to $r = .86$ for the individual domains; Rosen et al., 2000).

Beck Depression Inventory-II & Beck Anxiety Inventory. As both depression and anxiety are known to affect sexual functioning (e.g., Bossini, Fagiolini, Valdagno, Polizzotto, & Castrogiovanni, 2007; Williams & Reynolds, 2006) and depression is also associated with reduced endocannabinoid levels (Hill & Gorzalka, 2009; Hill et al., 2008; 2009), the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), 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 symptoms such as

guilt and hopelessness, physical symptoms such as fatigue and weight loss, and affective symptoms such as irritability and tearfulness. 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 (Beck et al., 1988, 1996; Osman, Downs, Barrios, Kopper, Gutierrez, & Chiros, 1997; Osman, Kopper, Barrios, Osman, & Wade, 1997; Storch, Roberti, & Roth, 2004) and have been used extensively in both clinical and research settings.

Continuous Measure of Subjective Arousal. A device identical to the one developed by Rellini et al. (2005), which the authors termed an "arousometer," was constructed and employed in this study to measure continuous subjective sexual arousal. This measure 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.

Procedure

Participants were recruited via advertisements posted throughout the campus of the University of British Columbia and the surrounding community. As in Experiment 1, advertisements sought out "medically healthy adult women for a study on the physiology of

female sexual arousal," and included information on eligibility and exclusion criteria and indicated that an honourarium in exchange for study participation would be provided.

The procedures for this study were identical to those used in Experiment 1 with a few exceptions. First, participants were screened over the telephone for eligibility to participate using the revised eligibility criteria. Second, the two sessions were scheduled on consecutive days (rather than one week apart as was done in Experiment 1) to try to ensure that both sessions took place during the same phase of the menstrual cycle. Third, participants were asked to fast on the morning of their sessions and to refrain from alcohol use in the previous 24 hours. Fourth, prior to inserting the vaginal photoplethysmograph in sessions 1 and 2, participants took part in the brief testing conditions interview and were asked to complete a questionnaire package containing the DSFI, FSFI, BDI-II, and BAI. Fifth, participants took part in the LIH exercise immediately prior to viewing the film stimuli/measuring their sexual arousal in each session. Lastly, during viewing of the film stimuli, participants were asked to continuously monitor and indicate their subjective feelings of sexual arousal with the use of the "arousometer."

The LIH protocol employed in the current study was identical to that used by Brotto and Gorzalka (2002) and Brotto, Klein, and Gorzalka (2009). The procedure involves two minutes of rapid, deep breathing at a rate of 30 breaths/minute. Subjects 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.

Data Analysis

As in Experiment 1, 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, and multivariate analyses of variance for repeated measures were used to investigate the effects of the video stimuli on the three indices of non-continuous subjective sexual arousal (subjective physiological sexual arousal, mental sexual arousal, and overall subjective sexual arousal). Also as in Experiment 1, Pearson product moment correlation coefficients were used to investigate the correlations between endocannabinoid (AEA and 2-AG) levels and physiological and subjective indices of sexual arousal.

HLM was used to examine whether moment-to-moment fluctuations in physiological sexual arousal (as measured by the vaginal photoplethysmograph) were associated with moment-to-moment changes in continuous subjective sexual arousal (as measured by the "arousometer"). As previously noted, HLM has a number of advantages over traditional general linear modeling techniques such as repeated measures ANOVA. In addition to being robust to missing data, it allows for unbalanced data sets in which data have been collected at unequal intervals or different time points for each individual. It also circumvents the repeated-measures ANOVA assumption of equal variances between all pairwise difference scores. Furthermore, by partitioning the variability in the outcome data into within and between sources, it leads to more accurate estimates of the relationship between predictors and outcomes, increasing the likelihood that these estimates can be replicated (Bryk & Raudenbaush, 1992).

HLM can be conceptualized as a set of person-specific regression lines, with measurement units (level 1) nested within individuals (level 2). In the present study, the level 1

equation was constructed as follows: Level 1: $(PA)_{ij} = \beta_{0j} + \beta_{1j}(SA)_{ij} + e_{ij}$. In this equation, momentary changes in subjective arousal were modeled as a linear function of momentary changes in physiological arousal, plus a residual error term, e_{ij},. $(PA)_{ij}$ and $(SA)_{ij}$ represent, respectively, the physiological sexual arousal rating and subjective sexual arousal rating at time *i* for individual *j*. The coefficients β_{0j} and β_{1j} represent, respectively, the person-specific intercept and slope for individual *j*. The intercept is the predicted physiological arousal of a participant whose subjective arousal is equal to her average score across time, and the slope represents the predicted change in physiological arousal associated with each unit increase in subjective arousal.

In the second, or between-person, stage of analysis, the goal is to determine whether the person-specific intercepts (β_{0j}) and slopes (β_{1j}) vary according to between-person characteristics; however, as this study was only concerned with the covariation between subjective and physiological arousal across time, rather than between-person moderators of this relationship, we fit an unconditional model, that is, one without any level-2 predictors:

Level 2: $\beta_{0j} = \gamma_{00} + U_{0j}$

$$\beta_{1j} = \gamma_{10} + U_{1j}$$

In these equations, γ_{00} and γ_{10} signify the mean intercept and slope, respectively, across all individuals. These are considered to be fixed, or constant. U_{0j} and U_{1j} are random error terms designating the specific amounts by which individual *j* deviates from these means.

As in Experiment 1, in all cases a *p* level of less than .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 (Table 4) and the DSFI (Table 5). 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; Beck et al., 1996), in the mild range for anxiety on the BAI (M = 10.81; SD = 10.86; Beck et al., 1988), 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].

Table 4
Experiment 2 Female Sexual Functioning Inventory (FSFI) Participant Scores (N = 21)

Subscale (possible range)	Participant Mean (*SD*)	Healthy Controls Reported by Rosen et al. (2000)
Desire (2-10)	7.2 (2.31)	6.9 (1.89)
Arousal (4-20)	16.6 (3.70)	16.8 (3.62)
Lubrication (4-20)	17.5 (2.46)	18.6 (3.17)
Orgasm (3-15)	11.4 (3.40)	12.7 (3.16)
Pain (3-15)	12.7 (2.20)	13.9 (2.79)
Satisfaction (3-15)	10.5 (3.57)	12.8 (3.03)

Note: Higher scores = increased sexual functioning.

Table 5
Experiment 2 Derogatis Sexual Functioning Inventory (DSFI) Participant Scores (N = 21)

	M	*SD*
Subscale		
Information	46.10	11.14
Experience	51.30	7.63
Drive	57.15	9.08
Attitude	55.19	9.98
Symptoms (Brief Symptom Inventory)	47.52	9.37
Affects	54.29	11.72
Gender Roles	51.43	9.10
Fantasy	52.81	13.75
Body Image	42.14	9.97
Satisfaction	46.95	10.31
Sexual Functioning Index (SFI)	507.35	45.03
Global Sexual Satisfaction Index (GSSI)	5.00	2.41

Note. Means for the subscales are based on raw scores that were converted to established percentile rankings (T scores); SFI = sum of the subscale T scores; GSSI = 1-item measure of sexual relationship satisfaction, where 0 = "could not be worse" and 8 = "could not be better."

Effects of Film Stimuli on Physiological and Subjective Sexual Arousal

As in Experiment 1, 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 [$t(20) = 2.26$, $p = .035$].

With respect to the three non-continuous indices of subjective sexual arousal (i.e., mental sexual arousal, subjective physiological 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.

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 once again leading to increased subjective sexual arousal as compared to the control condition.

Effects of Film Stimuli on Endocannabinoid Levels

Changes in endocannabinoid (AEA and 2-AG) levels from pre-film to post-film in the experimental and control conditions are presented in Table 6, separately for all twenty-one

participants, along with changes in physiological sexual arousal, non-continuous indices of subjective sexual arousal, and continuous subjective sexual arousal.

A significant decrease in AEA levels 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 levels 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 levels were observed from pre-film to post-film in the control condition [AEA: $t(20) = 0.43$, $p > .05$; 2-AG: $t(20) = 1.65$, $p > .05$].

Table 6

Changes in Endocannabinoid Levels, Physiological, and Subjective Sexual Arousal Over the Course of the Experimental and Control Films

	EXPERIMENTAL							CONTROL						
P	AEA	2-AG	VPA	PHYS	MEN	OVER	CON	AEA	2-AG	VPA	PHYS	MEN	OVER	CON
1	-0.05	3.23	-51.40	7	1	1	-	0.11	1.39	-9.74	0	0	0	-
2	-0.29	-9.67	71.16	24	10	4	3.69	-0.10	-0.83	-10.70	0	0	0	0.13
3	0.05	2.36	54.39	4	4	1	0.46	0.01	0.42	20.20	0	-1	0	-0.22
4	-0.10	1.33	157.29	8	7	1	1.18	-0.20	-21.69	12.16	6	-2	1	-0.03
5	-0.16	0.60	-11.51	16	26	5	2.71	0.05	-3.72	-1.38	0	-1	0	0.00
6	-0.06	-8.96	11.17	13	7	4	4.27	-0.19	-0.46	16.49	3	1	0	-0.23
7	-0.24	-6.90	32.55	9	18	4	3.79	-0.02	-4.37	-20.70	-2	-1	0	0.00
8	-0.16	-5.22	6.72	14	13	3	2.07	-0.18	5.43	1.61	-1	-5	-1	-0.04
9	-0.01	17.78	78.03	11	13	3	1.15	-0.03	-23.81	33.31	1	0	0	0.00
10	-0.01	-3.45	-47.49	18	14	4	2.11	-0.09	9.73	-19.74	-1	-6	0	-0.04
11	-0.36	-9.76	4.09	17	14	4	3.52	-0.28	-14.35	9.71	0	0	0	-0.06
12	-0.11	16.96	29.65	11	8	2	2.46	-0.29	-10.98	-9.34	8	-6	2	0.37
13	-0.20	-25.10	-30.69	19	12	5	3.94	0.00	-21.40	27.07	0	0	0	0.00
14	-0.21	-8.61	100.76	11	9	4	4.19	0.10	9.21	-12.39	0	-2	0	0.00
15	0.34	16.10	-35.05	7	7	1	0.00	0.87	3.24	-5.39	1	0	0	0.00
16	-0.06	17.57	50.62	9	6	1	3.30	-0.13	-21.43	-23.11	0	-1	0	0.00
17	-0.21	-6.23	9.63	13	13	3	4.44	-0.28	-7.81	21.51	-16	-7	-4	0.00
18	0.14	4.50	8.19	0	3	1	1.94	-0.27	-8.46	0.77	-1	-2	0	0.00
19	-0.70	-10.51	396.42	12	21	5	5.75	0.30	18.20	-13.89	0	-7	0	-0.46
20	0.13	-11.62	210.91	18	13	6	5.63	-0.50	-3.30	-38.83	-1	-3	1	0.07
21	-0.14	-0.11	48.62	6	3	0	4.02	0.54	7.41	-3.81	0	0	0	0.00

Note. EXPERIMENTAL = experimental condition; CONTROL = control condition; P = participant number; AEA = change in arachidonoylethanolamide from pre- to post-film in pmol/mL; 2-AG = change in 2-arachidonoylglycerol from pre- to post-film in pmol/mL; VPA = vaginal pulse amplitude % change over course of film; PHYS = non-continuous subjective physiological sexual arousal difference score from pre-film to post-film (possible range = -30 – +30); MEN = non-continuous mental sexual arousal difference score from pre-film to post-film (possible range = -36 – +36); OVER = non-continuous overall subjective sexual arousal difference score from pre-film to post-film (possible range = -6 – +6); CON = continuous subjective sexual arousal difference score (possible range = -9 – +9).

Relationship Between Endocannabinoids and Sexual Arousal

Pearson product moment correlations between endocannabinoid levels, physiological sexual arousal, and subjective indices of sexual arousal are presented in Table 7, 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 levels and changes in sexual arousal, as can be seen in Table 7, changes in AEA levels 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 levels decreased. Similarly, significant negative correlations were found in the experimental condition between changes in AEA levels 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 levels and changes in non-continuous overall subjective sexual arousal ($r = -.43$, $p = .052$). No significant correlation was found between changes in AEA levels and non-continuous subjective physiological sexual arousal ($p > .09$).

Table 7

Experiment 2 Means, Standard Deviations, and Correlations for the Relationship Between Endocannabinoids and 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.

*$p < .05$

^$p < .06$

As can be seen in Table 7, with respect to changes in 2-AG levels 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 levels 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 levels from pre-film to post-film and any measures of sexual arousal, whether physiological or subjective. Changes in 2-AG levels 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 levels and any of the subjective indices of sexual arousal in the control condition (see Table 7; all p's > .07).

Relationships Between Indices of Sexual Arousal

As can be seen in Table 7, Pearson product moment correlations between physiological sexual arousal (VPA) and non-continuous measures of subjective sexual arousal (mental sexual arousal, subjective physiological sexual arousal, and overall subjective sexual arousal) revealed no significant associations in either the experimental or control conditions (see Table 7; all p's > .20).

In contrast, the Pearson product moment correlation between physiological sexual arousal and continuous subjective sexual arousal revealed a significant positive relationship in the experimental condition (r = .46, p = .040); however, using HLM to examine the within-person correlation between moment-to-moment changes in physiological sexual arousal and moment-to-moment changes in

continuous subjective sexual arousal revealed that, across participants, continuous subjective sexual arousal did not significantly predict physiological sexual arousal (β = 0.002371, t = 1.76, p > .09).

In the control condition, the Pearson product moment correlation between physiological sexual arousal and continuous subjective sexual arousal was not significant ($p > .40$), nor did continuous subjective sexual arousal significantly predict physiological sexual arousal in the within-subjects HLM analysis (β = -0.001078, t = -1.28, $p > .20$).

With respect to relationships between non-continuous and continuous measures of subjective sexual arousal, Pearson product moment correlations in the experimental condition revealed a significant association between continuous subjective sexual arousal and non-continuous overall subjective sexual arousal ($r = .61$, $p = .004$). A marginally significant correlation was found between continuous subjective sexual arousal and non-continuous subjective physiological sexual arousal ($r = .43$, $p = .057$). No significant correlation was found between continuous subjective sexual arousal and non-continuous mental sexual arousal in the experimental condition ($p > .10$), and no significant relationships between continuous and any non-continuous measures of subjective sexual arousal were found in the control condition (all p's > .30).

Pearson product moment correlations between the three non-continuous measures of subjective sexual arousal revealed significant associations between all three indices in the experimental condition ($r = .77$, $p < .001$ for the relationship between mental sexual arousal and overall sexual arousal; $r = .77$, $p < .001$ for the relationship between subjective physiological sexual arousal and overall sexual arousal; $r = .55$, $p = .011$ for the relationship between mental sexual arousal and subjective physiological sexual arousal). In the control condition, the only significant correlation found was between subjective physiological sexual arousal and overall subjective sexual arousal ($r = .93$, $p < .001$).

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

In the experimental condition, changes in 2-AG levels 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 levels 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 levels, 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).

Other Significant Correlations Between Affect, Stress, Days Since Start of Last Menstruation, and Subjective Autonomic Arousal

Significant correlations between affect, stress, days since start of the most recent menstrual cycle, and subjective autonomic arousal in the experimental condition included: (1) a significant negative correlation between BAI scores and changes in anxiety over the course of the film stimuli, such that higher scores on the BAI were associated with smaller reductions in anxiety during the film (r = -.49, p = .024); (2) a significant positive correlation between BAI scores and changes in subjective autonomic arousal over the course of the film stimuli, such that higher scores on the BAI were associated with greater increases in subjective autonomic arousal during the film (r = .62, p = .003); and (3) a significant positive correlation between changes in positive affect and changes in subjective autonomic arousal over the course of the film stimuli, such that increased positive affect was associated with increased subjective autonomic arousal (r = .69, p = .001).

Significant correlations between affect, stress, days since the most recent menstrual cycle, and subjective autonomic arousal in the control condition included: (1) a significant positive correlation between changes in subjective autonomic arousal and subjective anxiety over the course of the film stimuli, such that reductions in anxiety over the course of the film were also associated with reductions in subjective autonomic arousal (r = .78, p < .001); and (2) a significant negative correlation between BDI-II depression scores and changes in subjective anxiety over the course of the film stimuli, such that increased BDI-II depression scores were associated with less of a reduction in anxiety during the film (r = .-.47, p = .030).

No other correlations between depression, anxiety, positive affect, negative affect, self-reported stress levels, days since the start of the most recent menstrual cycle, and subjective autonomic arousal during the film stimuli were found to be significant (all *p*'s > .05).

Discussion

In contrast to the findings of Experiment 1, the results of this experiment revealed significant associations between endocannabinoid levels and female sexual arousal. In fact, this study provides the first evidence to date of alterations in circulating endocannabinoid levels in direct relation to changes in not only *physiological*, but also *subjective* sexual arousal in women. AEA levels 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. Decreased 2-AG levels were significantly related to increased perceptions of physiological sexual arousal, overall subjective sexual arousal, and to increased continuous subjective sexual arousal. In other words, the findings were consistent between physiological and subjective measures that, as sexual arousal increased, endocannabinoid levels decreased. Supporting the conclusion that the drop in endocannabinoid levels was related specifically to increased sexual arousal, no significant changes in endocannabinoid levels were seen in the control condition.

The fact that relationships between circulating endocannabinoid levels and sexual arousal were found in this study supports the over-arching hypothesis of this line of research that the endocannabinoid system is associated with female sexual function. The nature of the association found in this study was, however, contrary to the original study hypotheses. Specifically, it was originally hypothesized that endocannabinoid levels 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 (Dawley et al., 1979; Goode, 1969; Halikas et al., 1982; Koff, 1974; Kolodny et al., 1979; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970), although no data on the direct effects of cannabis on objective sexual psychophysiology exist. In addition, initial animal studies of the effects of cannabinoid receptor agonists and antagonists also showed some support for a relationship between cannabinoids and *enhanced* sexual functioning (Gordon et al., 1978; Mani et al., 2001; Turley & Floody, 1981).

Alternately, the results of three, more recent animal studies have given support to the idea that cannabinoids may, in fact, be related to *decreased* sexual functioning (Ferrari et al., 2000; López et al., 2009, 2010). 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 (Dawley et al., 1979; Goode, 1969; Halikas et al., 1982; Koff, 1974; Kolodny et al., 1979; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970), 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., Wilson & Lawson, 1976). As discussed earlier, there are multiple reasons that individuals may perceive cannabis as sexually enhancing. These include that cannabis may increase sensation or perception (Abel, 1981; Dawley et al., 1979; Halikas et al., 1982), decrease anxiety/facilitate relaxation (Adams & Martin, 1996; Hathaway, 2003; Kolodny et al., 1979), slow the perception of time and increase attentional focus on the sexual situation (Gawin, 1978; Jarvik & Brecher, 1977; Lewis, 1970; Melges et al., 1971), reduce inhibitions (Dawley et al., 1979; Kolansky & Moore, 1972; Kolodny et al., 1979; McKay, 2005), or lead to

perceptions of enhanced sexual functioning through expectancy effects (Crenshaw & Goldberg, 1996; Rosen, 1991).

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, despite having twice the sample size of Experiment 1, nevertheless remained 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., Weiss, Beiras-Fernandez, Hauer, Hornuss, Sodian, Kreth, et al., 2010) and non-human species (e.g., Hill, McLaughlin, Bingham, Shrestha, Lee, Gray, et al., 2010). 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 (Basson, 2001, 2002a; Basson et al., 2000; 2003) have challenged the concept of physiological and subjective sexual arousal as inseparable events, and have instead proposed a new classification of female sexual arousal disorder that distinguishes physiological from subjective sexual arousal. 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, until further research replicates the results of this study with larger samples, this remains purely speculative.

An argument against this speculation is the finding of this study of concordance between subjective and physiological sexual arousal *when the former was assessed via a continuous measure of arousal* (i.e., the "arousometer"). As in past research, this study found a lack of concordance between physiological and subjective measures of sexual arousal when sexual arousal was measured via non-continuous pre- and post-film questionnaires. The finding of discordance when subjective sexual arousal was measured non-continuously, but of concordance when subjective sexual arousal was measured continuously, is partially in line with the hypothesis put forth by Rellini and colleagues (2005), in which they proposed that findings of low or no concordance are partially the result of the limited way in which subjective sexual arousal has been measured in the past—namely, via pre- and post-stimuli questionnaires that provide only two data points and that rely on retrospective recall. The results are also in line with a meta-analysis conducted by Chivers and colleagues (2010) which revealed that continuous measures of subjective sexual arousal increase concordance in women.

Noteworthy, however, is that Rellini and colleagues (2005) also suggested that past findings of discordance are not only the result of the limited way in which sexual arousal has generally been measured, but also the result of the use of statistical methods (i.e., correlational analyses) that reduce measures of arousal to only one data point, thereby greatly diminishing the richness of the data and the ability to study how moment-to-moment changes in one variable are associated with moment-to-moment changes in another. Rellini and colleagues (2005), therefore, suggested that HLM be used, and that doing so would result in concordance between these two variables. The results in the present study did not support this latter hypothesis. While significant Pearson's correlations, which are indicative of concordance, were found between continuously measured physiological and subjective sexual arousal, HLM did not result in a finding that subjective sexual arousal significantly predicted physiological sexual arousal.

It should be noted, however, that while the *average* within-subject correlation across participants was not significant in this study, there was considerable between-subject variance, suggesting that there are individual-level predictors that may moderate the strength of the relationship between physiological and subjective sexual arousal. As Rellini et al. (2005) concluded based on similar findings of considerable between-subject variance, investigating what moderates the strength of this relationship will be an important area for future study.

As this study found concordance between continuously measured subjective and physiological sexual arousal when analyzed via correlational analyses, but that HLM, in contrast, did not result in findings of concordance, the results of this study suggest that the continuous "arousometer" measure of arousal may be what is sufficient and necessary for detecting concordance (as opposed to the combination of the "arousometer" with the use of HLM). This does not, however, suggest that HLM analyses are not useful or informative. Traditional correlational analyses and HLM are addressing two different questions, and the results cannot truly be compared. Specifically, correlational analyses are between-subjects analyses in which the factor of "time" is completely eliminated by reducing scores to a single value. In contrast, HLM is a within-subjects analysis that takes the factor of "time" into account by preserving data collected at each time point and analyzing the change that is occurring within each individual across these time points. Thus, the fact that Pearson's correlations found a significant relationship between continuously measured subjective and physiological sexual arousal in this study, but that HLM did not find that continuously measured subjective sexual arousal predicted physiological sexual arousal, is not contradictory. Rather, it reveals that, while correlations between continuously measured subjective and physiological sexual arousal were significant when analyzed across participants, some participants' subjective and physiological scores co-varied strongly, while others' co-varied weakly or not at all, resulting in an average slope that was not significant.

With respect to the difference between continuous and non-continuous measures of subjective sexual arousal, it is interesting to note that subjective sexual arousal as measured by the "arousometer" did not always correlate significantly with subjective sexual arousal as measured by the Film Scales. This raises the question of what the arousometer is actually measuring. Rellini et al. (2005) concluded that the arousometer measures mental sexual arousal, as opposed to perceived physiological sexual arousal; however, this study did not find a significant relationship between continuously measured subjective sexual arousal and non-continuously measured mental sexual arousal. Instead, this study found a significant correlation between continuously measured subjective sexual arousal and non-continuously measured overall subjective sexual arousal, and a marginally significant correlation between continuously measured subjective sexual arousal and non-continuously measured perceived physiological sexual arousal. It should be noted, however, that Rellini et al. (2005) modified the Film Scale to be a 17-item, rather than a 34-item, measure, and that the disparity between the present findings and those of Rellini et al. (2005) may have been due to this difference. Because Rellini and her colleagues did not publish information on which items they dropped from the Film Scale (nor their rationale for doing so), it was not possible to re-analyze the results of this study using Rellini et al.'s modified version to test whether this difference was responsible for the discrepancy in findings.

This study did not find any significant relationships between endocannabinoids and factors which have previously been associated with endocannabinoid levels such as stress, depression, and anxiety (Gorzalka et al., 2008; Hill et al., 2008, 2009). 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 levels and affective states were conducted by comparing endocannabinoid levels 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.

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 levels. 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 levels 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.

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 (Abel, 1981; Dawley et al., 1979; Goode, 1969; Koff, 1974; National Commission on Marihuana and Drug Abuse, 1972), and that some research has found that individuals specifically use cannabis to try to facilitate sexual function (e.g., Bellis et al., 2008; Bouguet, 1950; Sumnall et al., 2007), the use of cannabis for this purpose may be counter-productive and even detrimental to sexual function.

Third, this study provides support for Rellini and colleagues' (2005) hypothesis that past findings of discordance in women may be the result of limitations in measurement instruments, rather than the result of true conceptual distinctions between subjective and physiological sexual arousal in women. Further research is needed to verify the reliability of findings of concordance when subjective sexual arousal is measured continuously. This research has importance to our understanding of female sexual arousal. Specifically, the repeated past findings of discordance in women have not only led to proposed changes to the way female sexual arousal is conceptualized and the way female sexual arousal disorder is diagnosed, but it has even led some to question whether physiological changes that occur in the absence of subjective sexual arousal should be classified as a sexual response (Basson, 2001, 2002a; Basson et al., 2000; 2003). The results of the current study suggest that women's sexual arousal may not, in fact, be discordant. Finally, related to the previous point, this study provides further support for the use of a continuous measure of sexual arousal (such as the "arousometer"; Rellini et al., 2005) in research measuring subjective sexual arousal and, in particular, in research examining the concordance between physiological and subjective sexual arousal in women.

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, is now needed.

Experiment 3: Marijuana Use and Sexual Arousal in Women

All studies conducted to date on the effects of cannabis use on sexual functioning in women have found an effect, with all but one of these studies (i.e., Johnson et al., 2004) showing a facilitatory, rather than an inhibitory, effect of cannabis on sexual function (Dawley et al., 1979; Goode, 1969; Halikas et al., 1982; Koff, 1974; Kolodny et al., 1979; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970). The specific effects suggested by these studies have ranged from effects on sexual desire, to effects on sexual arousal and orgasm. In addition, a number of ambiguous effects (i.e., pertaining to "sexual pleasure" or "satisfaction") have also been reported. However, because these studies utilized self-reported retrospective recall as a means of assessing sexual function, it is unknown whether the previously reported effects in women are due to physiological changes, to sexually non-specific effects of cannabis such as increases in tactile sensitivity or decreases in anxiety, or to altered perceptions and cognitions.

Therefore, the purpose of Experiment 3 was to examine the effects of prior cannabis consumption on not only subjective, but also physiological, sexual arousal in women. Further, as subjective reports in the human literature and observable effects in the non-human literature have suggested a dose-dependent relationship between cannabinoids and female sexual function (i.e., Gordon et al., 1978; Koff, 1974), this study set out to examine the effects of regular use of marijuana, as compared to less frequent/occasional use of marijuana, and to non-use of marijuana, on subjective and physiological sexual arousal. Based on the previous subjective self-report studies in humans and the studies in other species which found a facilitatory effect of cannabis on sexual function at low doses but detrimental effects at higher doses, it was hypothesized that women who smoke marijuana occasionally, including within the week prior to study participation, would show facilitated physiological sexual arousal compared to women who do not smoke marijuana. Conversely, it was further hypothesized that

women who smoke marijuana on a regular basis, including within the week prior to study participation, would show inhibited physiological sexual arousal compared to women who do not smoke marijuana. (These hypotheses were made before the results of Experiment 2 were available; in fact, Studies 2 and 3 were conducted concurrently).

Therefore, while the aim of Experiment 2 was to look at the effects of physiological and subjective sexual arousal *on endocannabinoid levels*, the aim of Experiment 3 was to examine the effects of exogenous cannabinoid (cannabis) use *on physiological and subjective sexual arousal* in women. This research expands on previous research by utilizing a physiological measure and by assessing frequency of use in the relationship between cannabis consumption and sexual arousal in women.

This study also had the same secondary aim as Experiment 2, which was to test/replicate the hypotheses and findings of Rellini et al. (2005) with respect to the relationship between physiological and subjective sexual arousal. As previously reviewed, Rellini and her colleagues (2005) proposed that measuring subjective sexual arousal continuously and simultaneously with physiological sexual arousal (rather than non-continuously before and after the presentation of erotic stimuli), and then analyzing the data via hierarchical linear modeling (HLM), may lead to findings of significant concordance, rather than discordance, between these two measures of sexual arousal. In other words, Rellini's research team hypothesized that subjective and physiological sexual arousal are not, in fact, two distinct entities, but rather that methodological and statistical shortcomings have resulted in past findings of discordance.

As previously mentioned, discerning whether subjective and physiological sexual arousal are two distinct constructs in women, or whether past methodological and statistical methods have hampered detecting a concordance between measures of the same underlying construct, has significant implications for the field of female sexuality. Specifically, the repeated findings in past research of a

lack of concordance between physiological and subjective measures of sexual arousal (e.g., Geer et al., 1974; Brotto et al., 2009; Laan & Everaerd, 1995; Laan et al., 1994, 1995; Morokoff & Heiman, 1980; Meston & Gorzalka, 1995; Palace & Gorzalka, 1990; 1992; Rosen & Beck, 1988; Steinman et al., 1981; Wincze et al., 1976) have resulted in proposed changes to the ways female sexual arousal and related difficulties are conceptualized (Basson, 2001, 2002a; Basson et al., 2000; 2003). If, however, physiological and subjective sexual arousal are both reflective of the same underlying construct, recommendations to delineate subtypes of female sexual arousal disorder may no longer be warranted.

Method

Participants

Forty-eight medically healthy, premenopausal women between the ages of 19-45 participated in this study. "Medically healthy" was once again defined as being in good physical health, with no history of chronic medical illnesses, no indications of current acute infections, no mental disorders, and no sexual dysfunctions.

The 48 women were comprised of three groups: The first group was composed of 17 women who had not used marijuana in the past six months (the "non-user" group). The second group was composed of 17 women who had used marijuana occasionally in the past six months, including within the week prior to study participation (the "occasional-user" group). Occasional use was defined as the use of marijuana once or twice per week. The third group consisted of 14 women who had used cannabis regularly within the past six months, including within the week prior to study participation (the "regular-user" group). Regular use was defined as the use of marijuana three or more times per week. While the differentiation between occasional and regular use is somewhat arbitrary, this differentiation has been used in previous research (e.g., Cuttler, McLaughlin, & Graf, 2007) and ensured that the sample was comprised of women with an adequate range of marijuana use to conduct comparisons between groups.

Other than the acceptability of marijuana use in groups two and three, the exclusion criteria for this study were identical to the exclusion criteria used in Experiment 2.

Demographic characteristics are presented in Table 8. No significant differences between groups were found for age, education, or ethnicity ($p > .05$); however, significant differences between groups were found for relationship status when participants were categorized as being either single or in a relationship (Pearson's $\chi^2 = 6.62$, $p = .037$). The standardized residuals for each cell revealed that more of the participants in the marijuana non-user group were single as opposed to in a relationship. The number of marijuana users (both occasional and frequent) who were single versus in a relationship was not significantly different from what would be expected.

Table 8
Experiment 3 Participant Characteristics (N = 48)

	Non-Users (*N* = 17)		Occasional Users (*N* = 17)		Regular Users (*N* = 14)	
	Mean (*SD*)	*n* (%)	Mean (*SD*)	*n* (%)	Mean (*SD*)	*n* (%)
Age	26.18 (7.19)		22.76 (5.17)		24.25 (4.88)	
Years of Education	15.12 (1.41)		15.12 (3.01)		15.11 (1.27)	
Ethnicity						
Caucasian		9 (52.9)		13 (76.5)		8 (57.1)
East Asian		5 (29.4)		4 (23.5)		2 (14.3)
South Asian		1 (5.9)		-		-
Other		-		-		2 (14.3)
Mixed		2 (11.8)		-		2 (14.3)
Relationship Status						
Single		11 (64.7)		4 (23.5)		5 (35.7)
Committed Relationship		3 (17.6)		11 (64.7)		6 (42.9)
Common-Law		1 (5.9)		1 (5.9)		2 (14.3)
Married		1 (5.9)		-		1 (7.1)
Separated		1 (5.9)		-		-
Divorced		-		1 (5.9)		-

Apparatus and Materials

The film stimuli, vaginal photoplethysmography system, non-continuous measures of subjective sexual arousal (Film Scales), and continuous measure of subjective sexual arousal ("arousometer") were the same as those used and described previously in Experiments 1 and 2. The only changes in apparatus and materials from Experiments 1 and 2 to Experiment 3 are the elimination of any materials pertaining to venipuncture and the addition of questions pertaining to marijuana use, described below.

Measure of Marijuana Use. This measure consisted of 31 items which assessed frequency and amount of marijuana use, problems and side effects associated with marijuana use, and the relationship between marijuana use and sexual function. This measure is comprised of 22 items from the Marijuana Screening Inventory – Experimental Version (MSI-X; Alexander, 2003) and nine items from a measure of frequency and amount of marijuana use developed and used by Cuttler et al. (2007).

Procedure

As in Experiments 1 and 2, participants were recruited through advertisements posted throughout the campus of the University of British Columbia and the surrounding community. Advertisements sought medically healthy adult women for a study on the relationship between marijuana use and female sexual arousal, and included information on eligibility and exclusion criteria, as well as that an honourarium in exchange for study participation would be provided.

Interested individuals who met all study criteria were invited to take part in one, 75-minute session. The procedures to induce and measure sexual arousal during the session were identical to those implemented in Experiment 2, with the only difference being that both the neutral (control) and erotic (experimental) film stimuli were shown within one session rather than across two sessions. Between films, participants were given a 30 minute rest period to allow arousal levels to return to baseline. During this rest period, participants were asked to complete the DSFI, FSFI, BAI, BDI-II, and the

measure of marijuana use. At the end of the session, all participants were debriefed and received a printout of their physiological sexual arousal profiles, as measured by the photoplethysmograph, as well as a $20.00 honourarium.

Data Analysis

Between-within ANOVA was used to examine the effects of the film manipulations and marijuana user status on sexual arousal. As in Experiments 1 and 2, Pearson's product moment correlations were used to examine the relationships between physiological and subjective indices of sexual arousal, and as in Experiment 2, HLM was used to examine whether moment-to-moment fluctuations in physiological sexual arousal (as measured by the vaginal photoplethysmograph) were associated with moment-to-moment changes in continuous subjective sexual arousal (as measured by the "arousometer"). Once again, in all cases a p level of less than .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 DSFI (see Table 9) and the FSFI (see Table 10). 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 = 8.73; SD = 8.29; Beck et al., 1996), in the mild range for anxiety on the BAI (M = 7.83; SD = 9.04; Beck et al., 1988), and within one standard deviation of the mean for healthy controls with respect to psychological symptoms on the BSI [M (T-score) = 43.48; SD = 9.45].

Table 9
Experiment 3 Derogatis Sexual Functioning Inventory (DSFI) Participant Scores (N = 48)

	M	*SD*
Subscale		
Information	45.77	8.10
Experience	48.13	9.33
Drive	54.35	10.33
Attitude	56.90	11.71
Symptoms (Brief Symptom Inventory)	43.48	9.45
Affects	47.85	11.16
Gender Roles	50.42	9.44
Fantasy	56.69	10.48
Body Image	40.75	14.55
Satisfaction	49.77	14.24
Sexual Functioning Index (SFI)	494.10	50.79
Global Sexual Satisfaction Index (GSSI)	5.33	1.73

Note. Means for the subscales are based on raw scores that were converted to established percentile rankings (T scores); SFI = sum of the subscale T scores; GSSI = 1-item measure of sexual relationship satisfaction, where 0 = "could not be worse" and 8 = "could not be better."

Table 10
Experiment 3 Female Sexual Functioning Inventory (FSFI) Participant Scores (N = 48)

Subscale (possible range)	*Participant Mean (SD)*	*Healthy Controls Reported by Rosen et al. (2000)*
Desire (2-10)	7.56 (1.74)	6.9 (1.89)
Arousal (4-20)	17.28 (2.22)	16.8 (3.62)
Lubrication (4-20)	18.62 (1.85)	18.6 (3.17)
Orgasm (3-15)	11.88 (2.81)	12.7 (3.16)
Pain (3-15)	13.08 (1.57)	13.9 (2.79)
Satisfaction (3-15)	10.51 (3.96)	12.8 (3.03)

Note: Higher scores = better sexual functioning.

When scores on the DSFI were analyzed by group using multivariate analysis of variance (MANOVA), a significant difference between the three groups was found [$F(22,66) = 1.74$, $p = .045$]. Follow-up with univariate analyses revealed significant differences between groups on the DSFI Information subscale [$F(2,43) = 3.52$, $p = .038$] and the DSFI Sexual Drive subscale [$F(2,43) = 13.71$, $p < .001$], with marijuana non-users scoring significantly higher on a measure of sexual knowledge than occasional marijuana users ($p = .038$), and with marijuana non-users self-reporting significantly lower sex drives than occasional and regular marijuana users (both p's $< .001$).

When scores on the FSFI, BDI-II, and BAI were analyzed by group, no significant differences between the three groups were found (all p's $> .05$). Group differences in sexual and affective characteristics are presented in Table 11.

Table 11
Experiment 3 Group Differences in Sexual and Affective Characteristics

Measure	Non-Users (N = 17)	Occasional Users (N = 17)	Regular Users (N = 14)
Derogatis Sexual Functioning Inventory			
Information	48.88 (7.09) [a]	42.25 (6.21)	47.36 (8.78)
Experience	46.82 (11.51)	48.41 (7.49)	49.36 (8.88)
Drive	46.06 (7.39) [b]	57.65 (10.13)	60.43 (6.97)
Attitude	54.76 (13.86)	55.71 (9.83)	60.93 (10.73)
Symptoms (Brief Symptom Inventory)	44.94 (9.22)	41.12 (10.12)	44.57 (8.98)
Affect	45.88 (11.67)	46.65 (11.38)	51.71 (10.02)
Gender Roles	51.18 (9.93)	50.00 (8.66)	50.00 (10.38)
Fantasy	53.94 (9.84)	56.82 (12.08)	59.86 (8.80)
Body Image	40.76 (16.27)	37.71 (13.02)	44.43 (14.30)
Satisfaction	50.41 (21.12)	48.35 (8.86)	50.71 (9.10)
Sexual Functioning Index (SFI)	482.35 (55.37)	485.06 (47.11)	519.36 (42.97)
Global Sexual Satisfaction Index (GSSI)	4.63 (1.96)	5.38 (1.63)	6.07 (1.27)
Female Sexual Function Index			
Desire	7.00 (1.97)	7.41 (1.77)	8.43 (1.02)
Arousal	17.23 (2.59)	16.75 (2.44)	17.93 (1.44)
Lubrication	18.62 (2.18)	18.40 (1.92)	18.86 (1.51)
Orgasm	11.77 (2.83)	11.31 (3.22)	12.64 (2.27)
Pain	13.20 (2.20)	13.07 (1.28)	13.00 (1.41)
Satisfaction	9.32 (4.74)	10.69 (3.32)	11.50 (3.74)
Beck Anxiety Inventory	7.65 (7.24)	9.47 (12.83)	6.07 (4.68)
Beck Depression Inventory	9.82 (8.21)	9.47 (9.89)	6.50 (6.10)

[a]Non-user group significantly different from the occasional-user group, $p < .05$.
[b]Non-user group significantly different from both the occasional- and regular-user groups, $p < .001$.

Self-Reported Effects of Marijuana Use on Sexual Function

Forty of the 48 participants reported that they had used marijuana at some point in their lives. Of these, 30 (75.0%) reported that marijuana improved their sexual experiences, although 6 (20.0%) of these 30 women reported that marijuana only "rarely" improved their sexual experiences. In contrast, 8 (26.7%) reported that marijuana improved their sexual experiences "occasionally," 5 (16.7%) reported that it did so "regularly," and 11 (36.7%) reported that it did so "very often."

On a question of the extent to which marijuana was perceived to have had a negative impact on sexual experiences, 21 (52.5%) of the 40 women with a history of marijuana use reported that it "never" had a negative impact on their sexual experiences, 7 (17.5%) reported that it "rarely" had a negative impact on their sexual experiences, 6 (15.0%) reported that it "occasionally" had a negative impact on their sexual experiences, and 6 (15.0%) reported that it "regularly" had a negative impact on their sexual experiences. None of the women reported that it had a negative impact on their sexual experiences "very often."

On a question asking those participants with a history of marijuana use whether they prefer to be high on marijuana when having sex, 2 (6.7%) responded "very often," 8 (26.7%) responded "regularly," 13 (43.3%) responded "occasionally," 9 (30.0%) responded "rarely," and 8 (26.7%) responded "never."

Effects of Film Stimuli and Marijuana User Status on Physiological Sexual Arousal

A between-within analysis of variance revealed a significant effect of film on physiological sexual arousal [$F(1,45) = 39.25$, $p < .001$]; however, this was qualified by a significant film by group interaction [$F(2,45) = 5.80$, $p = .006$]. Follow-up analyses revealed a significant effect of film (with physiological sexual arousal significantly greater in the experimental than in the control condition) for regular marijuana users [$F(1,13) = 11.56$, $p = .005$], and for marijuana non-users [$F(1,16) = 28.49$, $p <$

.001], but only a marginally significant effect of film for occasional marijuana users [$F(1,16) = 3.95$, $p = .064$]. There was no main effect of group ($p > .06$).

One-way analyses of variance showed no significant between-group differences in physiological sexual arousal change scores in the control condition ($p > .20$). In the experimental condition, there was a significant effect of group [$F(2,45) = 4.59$, $p = .015$], with Tukey's post-hoc comparisons revealing that marijuana non-users showed a significantly greater increase in physiological sexual arousal during the erotic film than occasional marijuana users ($p = .013$). There was no significant difference between either marijuana non-users and regular marijuana users ($p > .10$) or between occasional and regular marijuana users ($p > .65$). These results, as well as the results for non-continuous indices of subjective sexual arousal (i.e., mental sexual arousal, subjective physiological sexual arousal, and overall subjective sexual arousal), and continuous subjective sexual arousal, are presented in Table 12.

Table 12
Experiment 3 Group Differences (Means and SDs) in Physiological and Subjective Sexual Arousal

EXPERIMENTAL CONDITION						
	Non-Users (N = 17)		Occasional Users (N = 17)		Regular Users (N = 14)	
VPA[a]	123.79	(95.70)	47.21	(63.23)	70.72	(58.57)
PHYS	9.82	(6.78)	6.82	(5.39)	7.21	(5.04)
MEN	10.06	(9.44)	4.94	(6.70)	6.54	(5.74)
OVER	2.94	(1.78)	2.53	(1.55)	2.29	(1.49)
CON	2.41	(1.60)	2.54	(1.60)	2.17	(1.60)

CONTROL CONDITION						
	Non-Users (N = 17)		Occasional Users (N = 17)		Regular Users (N = 14)	
VPA	1.03	(12.96)	12.51	(28.09)	14.86	(25.93)
PHYS	-0.59	(2.65)	-1.41	(4.18)	-0.86	(3.59)
MEN	-2.29	(3.16)	-0.71	(4.21)	-4.00	(5.51)
OVER	0.00	(0.61)	-0.18	(1.07)	-0.21	(1.37)
CON	-0.03	(0.22)	-0.05	(0.57)	0.29	(0.86)

Note. VPA = vaginal pulse amplitude % increase over course of film; PHYS = non-continuous subjective physiological sexual arousal difference score (possible range = -30 – +30); MEN = non-continuous mental sexual arousal difference score (possible range = -36 – +36); OVER = non-continuous overall subjective sexual arousal difference score (possible range = -6 – +6); CON = continuous subjective sexual arousal difference score (possible range = -9 – +9).
[a]Non-user group significantly different from the occasional-user group, $p < .02$.

Effects of Film Stimuli and Marijuana User Status on Non-continuous Indices of Subjective Sexual Arousal

A between-within MANOVA did not reveal significant between-group differences with respect to the effects of film on non-continuous subjective sexual arousal [Wilk's λ $F(6,86) = 1.03$, $p > .40$], but did reveal an overall difference in subjective sexual arousal between the experimental and control films [$F(3,43) = 25.84$, $p < .001$]. Follow-up univariate tests revealed significant differences for non-continuous subjective physiological sexual arousal [$F(1,45) = 61.60$, $p < .001$], mental sexual arousal [$F(1,45) = 49.24$, $p < .001$], and overall subjective sexual arousal [$F(1,45) = 71.82$, $p < .001$], with the

experimental film leading to increased indices of non-continuous sexual arousal compared to the control film.

Multivariate analyses of variance showed no significant between-group differences in mental sexual arousal, subjective physiological sexual arousal, or overall subjective sexual arousal change scores in either the control [Wilk's λ $F(6,86) = 1.15$, $p > .30$], or the experimental [Wilk's λ $F(6,86) = 0.81$, $p > .55$] condition.

Effects of Film Stimuli and Marijuana User Status on Continuous Subjective Sexual Arousal

A between-within ANOVA did not show a significant group by film interaction for pre- to post-film change scores on the "arousometer" ($p > .50$); however, there was a significant main effect of film [$F(1,41) = 80.66$, $p < .001$], with the erotic film resulting in significantly greater increases in continuous subjective ratings of sexual arousal than the neutral film. There was no main effect of group ($p > .95$).

One-way analyses of variance showed no significant between-group differences in continuous subjective sexual arousal change scores in either the control or the experimental conditions (both p's $>$ .20).

Effect of Film Stimuli and Marijuana User Status on Autonomic Arousal, Anxiety, and Affect

Using Wilk's λ (MANOVA), no significant differences in self-reported autonomic arousal, anxiety, positive affect, or negative affect were seen between groups while watching either the erotic ($p > .50$) or the neutral ($p > .50$) film stimuli.

Effects of Film Stimuli and Marijuana User Status on Sexual Arousal When Participants were Re-Categorized into Marijuana Users versus Non-Users

Analyses were re-conducted combining occasional and regular marijuana users into one group of marijuana users, and comparing these to non-users. A between-within analysis of variance once again revealed a significant effect of film on physiological sexual arousal [$F(1,46) = 50.43$, $p < .001$], as well

as a significant effect of group [$F(1,46) = 5.01$, $p = .030$]. These main effects were again qualified by a significant film by group interaction [$F(1,46) = 11.14$, $p = .002$]. Follow-up analyses revealed a significant effect of film (with physiological sexual arousal significantly greater in the experimental than in the control condition) for both marijuana users [$F(1,30) = 13.44$, $p = .001$], and for marijuana non-users [$F(1,16) = 28.49$, $p < .001$].

One-way analyses of variance showed no significant between-group differences in physiological sexual arousal change scores in the control condition ($p > .08$). However, in the experimental condition, there was a significant effect of group [$F(1,46) = 8.48$, $p = .006$], with marijuana non-users evidencing a significantly greater increase in physiological sexual arousal during the erotic film than marijuana users. These results, as well as the results for non-continuous indices of subjective sexual arousal (i.e., mental sexual arousal, subjective physiological sexual arousal, and overall subjective sexual arousal), and continuous subjective sexual arousal, are presented in Table 13.

As had been found when marijuana users were divided into occasional- and regular-users, a between-within MANOVA did not reveal significant between-group differences with respect to the effects of film on non-continuous subjective sexual arousal when marijuana users were grouped together and compared to non-users [Wilk's λ $F(3,44) = 1.62$, $p > .15$]. Multivariate analyses of variance showed no significant between-group differences in mental sexual arousal, subjective physiological sexual arousal, or overall subjective sexual arousal change scores in either the control [Wilk's λ $F(3,44) = 0.20$, $p > .85$], or the experimental [Wilk's λ $F(3,44) = 1.33$, $p > .25$] condition.

A between-within ANOVA also did not show a significant group by film interaction for pre- to post-film change scores on the "arousometer" ($p > .75$), nor a main effect of group ($p > .85$). One-way analyses of variance showed no significant between-group differences in continuous subjective sexual arousal change scores in either the control or the experimental conditions (both p's $> .50$).

Table 13

Experiment 3 Group Differences (Means and SDs) in Sexual Arousal when Participants were Categorized into Marijuana Users versus Non-Users

	EXPERIMENTAL CONDITION	
	Non-Users (N = 17)	Marijuana Users (N = 31)
VPA[a]	123.79 (95.70)	57.83 (61.32)
PHYS	9.82 (6.78)	7.00 (5.15)
MEN	10.06 (9.44)	5.66 (6.24)
OVER	2.94 (1.78)	2.42 (1.50)
CON	2.41 (1.60)	2.38 (1.59)

	CONTROL CONDITION	
	Non-Users (N = 17)	Marijuana Users (N = 31)
VPA	1.03 (12.96)	13.57 (26.71)
PHYS	-0.59 (2.65)	-1.16 (3.87)
MEN	-2.29 (3.16)	-2.19 (5.04)
OVER	0.00 (0.61)	-0.19 (1.19)
CON	-0.03 (0.22)	0.10 (0.68)

Note. VPA = vaginal pulse amplitude % increase over course of film; PHYS = non-continuous subjective physiological sexual arousal difference score (possible range = -30 – +30); MEN = non-continuous mental sexual arousal difference score (possible range = -36 – +36); OVER = non-continuous overall subjective sexual arousal difference score (possible range = -6 – +6); CON = continuous subjective sexual arousal difference score (possible range = -9 – +9).

[a]Non-user group significantly different from the marijuana-user group, $p < .01$.

Effects of Acute Marijuana Use on Sexual Arousal, Autonomic Arousal, Anxiety, and Affect

Of the 31 marijuana-using participants in this study, 8 (25.8%) reported coming to the session under the influence of marijuana. Of these, 7 belonged to the regular-user group and 1 belonged to the occasional-user group. Using Wilk's λ (MANOVA), coming to the session under the influence of marijuana was not found to be associated with significant differences in physiological or subjective indices of sexual arousal as compared to participants who were not under the influence ($p > .35$). Similarly, coming to the session under the influence of marijuana was not associated with significant differences in self-reported autonomic arousal, anxiety, positive affect, or negative affect while watching the film stimuli in the experimental or control conditions ($p > .45$).

Relationships Between Physiological and Subjective Indices of Sexual Arousal for the Overall Sample

Pearson product moment correlations between physiological and subjective indices of sexual arousal for the sample as a whole are presented in Table 14. As can be seen in Table 14, significant correlations in the experimental condition were found between physiological sexual arousal and non-continuous subjective physiological sexual arousal ($r = .42$, $p = .003$), as well as between physiological sexual arousal and continuous subjective sexual arousal ($r = .31$, $p = .038$). A marginally significant correlation was found between physiological sexual arousal and non-continuous mental sexual arousal ($r = .26$, $p = .059$). There was no significant correlation between physiological sexual arousal and non-continuous overall subjective sexual arousal ($p > .09$).

In the control condition, physiological sexual arousal was not significantly associated with any of the subjective indices of sexual arousal, whether continuous or non-continuous (all ps $> .20$).

Table 14

Experiment 3 Means, Standard Deviations, and Correlations for the Relationship Between Physiological and Subjective Sexual Arousal for the Entire Sample

EXPERIMENTAL CONDITION

Variables	PHYS	MEN	OVER	CON	*M*	*SD*
VPA	.42*	.28^	.24	.31*	81.19	80.84
PHYS	__	.61*	.60*	.55*	8.00	5.87
MEN	__	__	.52*	.39*	7.22	7.72
OVER	__	__	__	.51*	2.60	1.61
CON	__	__	__	__	2.39	1.57

CONTROL CONDITION

Variables	PHYS	MEN	OVER	CON	*M*	*SD*
VPA	.01	-.19	.01	.01	9.13	23.44
PHYS	__	.39*	.82*	.17	-0.96	3.47
MEN	__	__	.54*	.08	-2.23	4.43
OVER	__	__	__	.31*	-0.13	1.02
CON	__	__	__	__	0.06	0.57

Note. 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.

*$p < .05$

^$p < .06$

HLM analyses used to examine the within-subjects correlation between moment-to-moment changes in physiological sexual arousal and moment-to-moment changes in continuous subjective sexual arousal in the experimental condition revealed that continuous subjective sexual arousal significantly predicted physiological sexual arousal ($\beta = 0.009160$, $t = 5.58$, $p < .001$) for the overall sample. In contrast, continuous subjective sexual arousal did not significantly predict physiological sexual arousal in the control condition ($\beta = 0.001038$, $t = .81$, $p > .40$).

With respect to relationships between non-continuous and continuous measures of subjective sexual arousal, Pearson product moment correlations for the experimental condition revealed significant correlations between continuous subjective sexual arousal and non-continuous mental arousal ($r = .39$, $p = .009$), as well as between continuous subjective sexual arousal and non-continuous subjective physiological sexual arousal ($r = .55$, $p < .001$), and between continuous subjective sexual arousal and non-continuous overall subjective sexual arousal ($r = .51$, $p < .001$). In the control condition, continuous subjective sexual arousal was significantly associated with non-continuous overall subjective sexual arousal ($r = .31$, $p = .041$), but not with either non-continuous mental sexual arousal ($p > .60$) or non-continuous subjective physiological sexual arousal ($p > .25$).

Pearson product moment correlations between the three non-continuous measures of subjective sexual arousal revealed significant associations between all three indices in the experimental condition ($r = .52$, $p < .001$, for the relationship between mental sexual arousal and overall sexual arousal; $r = .60$, $p < .001$, for the relationship between subjective physiological sexual arousal and overall sexual arousal; $r = .61$, $p < .001$, for the relationship between mental sexual arousal and subjective physiological sexual arousal), as well as in the control condition ($r = .54$, $p < .001$, for the relationship between mental sexual arousal and overall sexual arousal; $r = .82$, $p < .001$, for the relationship between subjective

physiological sexual arousal and overall sexual arousal; $r = .39$, $p = .006$, for the relationship between mental sexual arousal and subjective physiological sexual arousal).

Relationships Between Physiological and Subjective Indices of Sexual Arousal by Group

Pearson product moment correlations between physiological and subjective indices of sexual arousal when participants were divided into non-users, occasional users, and regular users are presented in Table 15. As can be seen in Table 15, there were differences between groups with respect to which correlations were significant. In particular, the two groups of marijuana users showed significant correlations in several instances in which non-users did not. For example, while the correlations between physiological and subjective physiological sexual arousal in the experimental condition were significant for both occasional and regular marijuana users, this correlation was not significant for non-users.

However, when Fisher *r*-to-*z* transformations were conducted in order to examine whether these differences in correlations between groups were statistically significant, the only correlations in the experimental condition that were significantly different between user groups were the correlations for physiological sexual arousal and continuous subjective sexual arousal, which were significantly different between marijuana non-users and regular users ($z = -2.43$, $p = .015$). Marginally significant differences were found between occasional and regular marijuana users for the correlations pertaining to non-continuous overall subjective sexual arousal and continuous subjective sexual arousal ($z = 1.92$, $p = .055$), and between marijuana non-users and regular users for the correlations pertaining to mental sexual arousal and overall subjective sexual arousal ($z = -1.94$, $p = .052$). These significant differences in correlations are signified via superscript letters in Table 15.

In the control condition, the only correlations that were significantly different between user groups were 1) the correlations for subjective physiological sexual arousal and mental sexual arousal, which were significantly different between marijuana non-users and occasional users ($z = -3.43$, $p =$

.001); and 2) the correlations for mental sexual arousal and overall subjective sexual arousal, which were significantly different between marijuana non-users and occasional users (z = -3.66, p < .001), and between marijuana non-users and regular users (z = -2.08, p = .038). These significant differences in correlations are once again signified via superscript letters in Table 15.

When occasional and regular marijuana users were combined into one group of marijuana users, no significant differences between correlations in the experimental condition between marijuana users and non-users were found. In the control condition, the correlations between subjective physiological sexual arousal and mental sexual arousal remained significantly different between non-users and users (z = -2.69, p = .007), as were the correlations between mental sexual arousal and overall subjective sexual arousal (z = -2.92, p = .004).

HLM analyses used to examine the correlation between moment-to-moment changes in physiological sexual arousal and moment-to-moment changes in continuous subjective sexual arousal in the experimental and control conditions did not reveal any differences between groups whether participants were divided into non-users, occasional users, and regular users, or whether participants were divided into only two groups of non-users and users (both p's > .05).

Table 15

Experiment 3 Means, Standard Deviations, and Pearson's Correlations for the Relationship Between Physiological and Subjective Sexual Arousal by Marijuana User Group

EXPERIMENTAL CONDITION

	PHYS			MEN			OVER			CON		
Variables	N	O	R	N	O	R	N	O	R	N	O	R
VPA	.17.	.62*	.53*	.08	.41	.14	.15	.41	.09	.12[a]	.40	.80*
PHYS	__	__	__	.43	.74*	.76*	.63*	.52*	.62*	.48	.53*	.77*
MEN	__	__	__	__	__	__	.36[b]	.56*	.82*	.35	.44	.48
OVER	__	__	__	__	__	__	__	__	__	.46	.77*	.24[c]
CON	__	__	__	__	__	__	__	__	__	__	__	__

CONTROL CONDITION

	PHYS			MEN			OVER			CON		
Variables	N	O	R	N	O	R	N	O	R	N	O	R
VPA	.26	.08	-.49	.03	-.01	-.46	.29	.16	-.17	.26	.02	-.10
PHYS	__	__	__	-.27[d]	.77*	.45	.81*	.94*	.74*	.55*	.14	.14
MEN	__	__	__	__	__	__	-.16[e]	.84*	.59*	-.33	.42	.12
OVER	__	__	__	__	__	__	__	__	__	.55*	.13	.43
CON	__	__	__	__	__	__	__	__	__	__	__	__

Note. 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; N = non-user group; O = occasional-user group; R = regular-user group.

*$p < .05$

[a]Correlation significantly different from the correlation for regular users, $p < .05$

[b]Correlation marginally significantly different from the correlation for regular users, $p < .06$

[c]Correlation marginally significantly different from the correlation for occasional users, $p < .06$

[d]Correlation significantly different from the correlation for occasional users, $p < .05$

[e]Correlation significantly different from the correlations for both occasional and regular users, $p < .05$

Discussion

The current study provides the first evidence to date of differences in physiological sexual arousal between marijuana users and non-users. This study found that while erotic film stimuli elicited significant increases in physiological sexual arousal in women who had not used marijuana in the last six months, and in women who had used marijuana regularly over this time period (i.e., three or more times per week), erotic film stimuli evoked only a *marginally* significant increase in physiological sexual arousal in women who used marijuana occasionally (i.e., no more than once or twice per week). Further, this study found a significantly lower increase in physiological sexual arousal during the erotic film in occasional marijuana users than in non-users. When occasional and regular marijuana users were subsequently combined into one group of marijuana users, and then compared to non-users, this also resulted in findings of significant differences in physiological sexual arousal between groups, with non-users exhibiting significantly greater increases in physiological sexual arousal during the erotic film than marijuana users. In contrast, no significant differences between marijuana user groups were seen on any of the subjective indices of sexual arousal.

The results of this study not only add to the evidence in support of cannabis' effects on sexual function and, by extension, the potential role of the endocannabinoid system in female sexual function, but also support past findings that the effects of cannabinoids on sexual function may vary by amount used. The effects of frequency of use on physiological sexual arousal in this study were, however, contrary to the original hypotheses: based on past research that found that self-reported sexual desire is highest after smoking one marijuana joint, but lessens with additional joints (Koff, 1974), and based on research in female rats that THC facilitates sexually receptive behaviours at low doses but impairs sexual receptivity at high doses (Gordon et al., 1978), it was hypothesized that occasional marijuana users would exhibit the greatest increase in physiological sexual arousal in response to erotic film

stimuli. The results of this study, however, indicate the opposite—occasional marijuana users exhibited the lowest increase in physiological sexual arousal.

The findings of this study are in line with more recent animal studies revealing that cannabinoid agonists (including THC) decrease sexual motivation, receptivity, and proceptivity in female rats, and that cannabinoid antagonists facilitate these behaviours (Ferrari et al., 2000; López et al., 2009, 2010). Further, these results are in line with literature which has shown that while individuals may report enhanced sexual functioning while under the influence of certain psychotropic substances, these substances are often, in reality, associated with decreased physiological sexual functioning (e.g., Wilson & Lawson, 1976). As previously discussed, multiple hypotheses exist for why individuals may perceive cannabis as a sexually enhancing substance, including that cannabis may increase sensation or perception (Abel, 1981; Dawley et al., 1979; Halikas et al., 1982), may decrease anxiety/facilitate relaxation (Adams & Martin, 1996; Hathaway, 2003; Kolodny et al., 1979), may slow the perception of time and increase attentional focus on the sexual situation (Gawin, 1978; Jarvik & Brecher, 1977; Lewis, 1970; Melges et al., 1971), may reduce inhibitions (Dawley et al., 1979; Kolansky & Moore, 1972; Kolodny et al., 1979; McKay, 2005), or may lead to perceptions of enhanced sexual functioning through expectancy effects (Crenshaw & Goldberg, 1996; Rosen, 1991).

It must be noted, however, that the current study was correlational in nature and that no causal conclusions regarding the effects of marijuana use on sexual function can, thus, be made. It is possible that differences in physiological sexual arousal between marijuana users and non-users existed *before* marijuana users ever began using marijuana. For example, it is possible that women with diminished sexual arousal are more likely to use marijuana, perhaps in an effort to increase arousal. Alternatively, it is also possible that a third, unrecognized variable is accounting for the reduced physiological sexual arousal seen in marijuana users.

An interesting finding in this study was that, while physiological sexual arousal was reduced in occasional marijuana users, regular marijuana users did not differ from either non-users or occasional users on this outcome. One possibility for this finding is that habituation or desensitization of the endocannabinoid system may occur with repeated marijuana use such that, over time, marijuana no longer produces the same detrimental effects on sexual function and/or on the endocannabinoid system in a regular user as is seen in occasional users. This, however, is purely speculative and requires in-depth investigation. At the same time, when occasional and regular marijuana users were combined into one group of marijuana users, and compared to non-users, significant differences between marijuana users and non-users remained, with non-users evidencing greater increases in physiological sexual arousal in response to the erotic film stimuli than marijuana users.

It must also be recognized that it is possible that an even stronger effect exists with respect to the relationship of marijuana use and physiological (and/or subjective) sexual arousal than was found in this study, given that this study specifically excluded women with sexual difficulties. While this exclusion was necessary in order to avoid spurious correlations between sexual function and cannabis use, this exclusion criterion may also have inadvertently skewed the results toward non-significance by potentially excluding women from the study who experience significant impairments in sexual arousal as a result of marijuana use.

As mentioned, no differences between marijuana user groups on subjective indices of sexual arousal were found in this study. This may be due to the fact that the majority of women in this study were not under the influence of marijuana at the time of study participation. Specifically, it is possible that increased subjective sexual arousal is only associated with acute marijuana use. At the same time, this study did not find a significant difference between either subjective or physiological sexual arousal in women who did present to the study session under the influence of marijuana, as compared to those

who did not; however, as seven of the eight women who attended the session under the influence belonged to the regular marijuana user group, *if* regular users do, in fact, habituate to the effects of cannabis on sexual function, this could explain why no significant differences were seen either between participants who were high versus those who were not, or between participants in the regular, occasional, and non-marijuana user groups.

Alternative possibilities for the lack of significant differences in subjective sexual arousal in marijuana users versus non-users include that the sample size in this study may have been insufficient to detect significant differences on subjective measures of arousal which generally have a higher error variance than physiological measures. Additionally, the ways in which "occasional" and "regular" users were defined may have masked significant findings. Specifically, this study utilized the definitions put forth by Cuttler et al. (2007); however, the delineation of what constituted an "occasional" and a "regular" user was reportedly made somewhat arbitrarily by Cuttler et al., who employed the current definitions in order to ensure that samples were comprised of women with an adequate range of marijuana use to conduct comparisons between groups. It is possible, however, that some of the occasional users were closer, in practice, to non-users or, alternatively, that some of the occasional users were closer in threshold to regular users, thereby skewing the results and potentially masking differences. Similarly, it is possible that different results would have been obtained if "regular" users had been defined as women who used marijuana even more frequently than was required for cut-off in this group.

While no differences between marijuana user groups were seen on subjective indices of sexual arousal in response to the erotic film, the majority (75%) of women in this study who had used marijuana at some point in their lives reported that marijuana improved their past sexual experiences. This finding is consistent with past research conducted on the self-reported effects of marijuana use on

sexual function (Dawley et al., 1979; Goode, 1969; Halikas et al., 1982; Koff, 1974; Kolodny et al., 1979; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970), notwithstanding one study by Johnson and colleagues (2004). What is interesting in this study, however, is that when also asked whether marijuana ever resulted in perceived *negative* effects on sexual experiences, almost half of the women with a history of ever having used marijuana responded affirmatively. Thus, although more women reported that marijuana resulted in beneficial than detrimental effects on sexual function, a significant number of these women also indicated that marijuana, at least sometimes, also resulted in negative sexual effects. This suggests that perceived positive sexual effects do not rule out the possibility of concurrent negative sexual effects—something which is particularly relevant to studies such as this one, where physiological differences in sexual arousal are found in the absence of corresponding subjective differences. Thus, future research may achieve greater insights into the complex effects of cannabis (and other drugs) on sexual function by assessing both positive *and* negative effects and, thereby, not assuming that the presence of positive effects denotes an absence of negative effects.

Also consistent with the results of a number of past studies (Dawley et al., 1979; Goode, 1969; Koff, 1974; National Commission on Marihuana and Drug Abuse, 1972; Smith et al., 2010; Tart, 1970) was the specific finding in this study that marijuana users (both occasional and regular) reported higher overall sex drives (i.e., sexual desire) than non-users. Unfortunately, without specific research assessing the specific relationship of the endocannabinoid system to sexual *desire*, it is unclear to what extent marijuana contributes to these heightened sexual drives either directly or indirectly, or whether the association between marijuana and sexual drive is due to a third variable. For example, it is possible that women with higher sexual drives are more likely to use marijuana to further enhance their sexual experiences. Alternatively, another plausible hypothesis is that women who are more liberal are not only

the ones who are most likely to use marijuana, but are also the ones most likely to take part in studies pertaining to sexuality and the ones most likely to report high sex drives due to less self-imposed constraints on acknowledging and openly expressing sexual desires.

The second aim of this study, as with Experiment 2, was to test Rellini et al.'s (2005) hypothesis regarding synchrony between physiological and subjective measures of sexual arousal in women. As in Experiment 2, the current study revealed a significant Pearson's correlation between physiological sexual arousal and continuously measured subjective sexual arousal in the experimental condition. This, once again, provides support that using the "arousometer" results in greater findings of concordance between physiological and subjective sexual arousal than would be found with non-continuous measures of subjective sexual arousal.

When concordance via Pearson's correlations was analyzed by group, marijuana users (both occasional and regular) had a greater number of significant correlations than non-marijuana users; however, the majority of the differences in correlations between user groups were not statistically significant. The only exceptions to this in the experimental condition were the correlations between continuously measured physiological and subjective sexual arousal, which were significantly greater in regular users than in non-users. A marginally significant difference in the correlations between mental sexual arousal and overall subjective sexual arousal was also found, with regular users again revealing a significantly greater correlation than non-users. This may suggest that regular users are better able to detect changes in physiological sexual arousal than non-users (perhaps as a result of heightened sensation/perception); however, given that only one set of correlations was significantly different between these two groups, and the other only marginally significant, further research investigating this possibility is needed.

Finally, with respect to the use of HLM to analyze the concordance between moment-to-moment changes in continuously measured physiological and subjective sexual arousal, results from this study revealed that continuous subjective sexual arousal significantly predicted physiological sexual arousal for the overall sample in the experimental condition. This result was not found in the control condition, nor were any significant differences found by group in either the experimental or control conditions for HLM-analyzed concordance. As previously discussed, HLM has significant benefits over traditional correlational methods of assessing concordance in women, such as preserving the richness of the data (see Rellini et al., 2005), and provides information that correlational analyses cannot.

As with Experiment 2, the results of this study have numerous important implications and highlight further areas for study. Specifically, these results are congruent with those of Experiment 2 that heightened sexual arousal is *not* associated with greater cannabinoid activity (in contrast to what was originally hypothesized to be the case). In fact, occasional cannabis use in this study was associated with *inhibited* physiological sexual arousal when compared to physiological sexual arousal of non-users, and marijuana use when occasional and regular users were combined into one group was also associated with inhibited physiological arousal compared to non-users. Therefore, based on the current study (and the results of Experiment 2), the reputation of cannabis as a drug that enhances sexual function (e.g., Abel, 1981; Dawley et al., 1979; Goode, 1969; Koff, 1974; National Commission on Marihuana and Drug Abuse, 1972) does not appear to be warranted—at least not with respect to physiological sexual arousal in women. In fact, as was previously suggested, the use of cannabis for the specific purpose of increasing sexual function may not only be ineffective, but possibly even detrimental to sexual function. It is, of course, still possible that cannabis has facilitatory effects on other phases of sexual response, such as sexual desire and orgasm. Research specifically focused on these sexual outcomes is needed in order to fully elucidate the role of the endocannabinoid system in female sexual function.

An interesting area for further study would be the investigation of the effects of dose- and potency-controlled acute marijuana use on physiological (and subjective) sexual arousal. However, considerable ethical limitations associated with conducting human research using prohibited substances make this particular research protocol difficult to implement. Another line of research that may be more feasible, however, and that would also shed considerable light on the potential role of the endocannabinoid system in female sexual functioning, is research examining the effects of cannabinoid receptor antagonists on physiological sexual arousal in women. As previously reviewed, this research has been conducted in non-human species with contradictory results across studies. Thus, research with cannabinoid antagonists in women may help to clarify past discrepant findings.

Finally, this study, like Experiment 2, provides support for Rellini and colleagues' (2005) hypothesis that past findings of discordance in women may be the result of limitations in measurement instruments, rather than the result of true conceptual distinctions between subjective and physiological sexual arousal in women. Based on these results, is recommended that continuous measures of sexual arousal be utilized in future research on sexual arousal in women.

General Discussion

Evidence from several lines of research has been pointing to the potential role of the endocannabinoid system in female sexual functioning. This evidence includes results from studies describing the effects of exogenous cannabinoids on sexual functioning in humans and 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.

The current research provides further support for an association between the endocannabinoid system and female sexual function. This research provides the first evidence that viewing erotic film stimuli results in a significant effect on endocannabinoids, specifically a decrease in circulating AEA. Further, increases in both physiological and subjective sexual arousal are associated with decreases in AEA, and increases in subjective sexual arousal are associated with decreases in 2-AG. This research also provides the first evidence to date of significant differences in physiological sexual arousal between women who do and those who do not use marijuana. Specifically, this research found that women who use marijuana occasionally show only a marginally significant increase in physiological sexual arousal in response to viewing erotic film stimuli, and that this increase in physiological sexual arousal is significantly less than the increase seen in women who do not use marijuana. Further, when occasional and regular marijuana users are combined to form one group of marijuana users, and then compared to non-users, the significant difference between marijuana non-users and users remains. This research utilizing physiological measures of arousal and direct measurement of endocannabinoid activity is paramount, given that past studies with women have solely utilized self-report and that one of the limitations of self-report is that the validity of responses cannot be verified without additional, physiological assessment.

Together, the findings of the current research suggest that activation of the endocannabinoid system is related to inhibited sexual arousal, and that the endocannabinoid system may play a modulatory role in female sexual function. The finding that enhanced sexual arousal in women appears to be associated with *decreased* circulating endocannabinoid levels, and that exogenous cannabis use is, similarly, associated with *reduced* physiological sexual arousal is contrary to the original hypotheses put forth for this research that elevated endocannabinoid levels, and moderate use of exogenous cannabinoids, would be associated with *increased* sexual arousal. In retrospect, however, the findings of this research are not altogether surprising, nor are they inconsistent with literature on the sometimes contrasting effects of psychotropic substances on subjective versus physiological sexual arousal. Such research has found that the subjective and physiological effects of psychotropic substances can be in direct contrast to each other, with subjective reports of enhanced sexual function being found together with physiological findings of reduced sexual function. Differential effects on sexual arousal have also been seen in other areas of research, such as research investigating the effects of anxiety on sexual arousal. This research has revealed that anxiety can increase physiological sexual arousal while simultaneously decreasing subjective sexual arousal in women (Palace & Gorzalka, 1990, 1992). The results of the current research are also consistent with recent animal studies that have shown a positive effect of cannabinoid receptor antagonists on sexual behaviour, and a negative effect of cannabinoid receptor agonists (Ferrari et al., 2000; López et al., 2009, 2010).

Given that depression is often associated with decreased sexual functioning, the fact that the present research found that heightened sexual arousal is associated with decreased endocannabinoid levels while the findings of Hill et al. (2008; 2009) found that major depression in women is also associated with decreased endocannabinoid levels may appear contradictory. However, Hill and colleagues did not require their participants to fast prior to study participation. As a result, if participants

in their study consumed calories prior to study participation, this would have resulted in decreased endocannabinoid levels. Further, given that depression can be associated with increased (although also decreased) appetite and food intake, it is possible that Hill et al.'s sample of depressed women consumed more before the session than control women, thus accounting for the significant differences between endocannabionoid levels in their depressed versus their non-depressed groups of women. Perhaps more importantly, it must be recognized that the relationship between depression, neurochemistry, and sexual function is complex. For example, while depression is often associated with impairments in sexual function, pharmacological treatments which alleviate depression are, similarly, frequently associated with impaired sexual functioning. Thus, the findings by Hill et al. (2008, 2009) of reduced endocannabinoid levels in women with major depression are not, necessarily, in conflict with the findings in the current research of reduced endocannabinoid levels in response to increases in physiological sexual arousal, as the potential roles of the endocannabinoid system in depression and sexual function are likely complex and affected by a multitude of factors.

The current research was novel in its approach to investigating the potential role of the endocannabinoid system in female sexual arousal. All three experiments measured not only subjective, but also physiological, sexual arousal. Experiments 1 and 2 measured serum endocannabinoid levels in relation to changes in subjective and physiological sexual arousal. Experiments 1 and 2 belong to only a handful of studies to date which have examined the relationship between circulating endocannabinoids and behavioural measures (i.e., Hill et al., 2008; 2009; Jumpertz, Wiesner, Blüher, Engeli, Bátkai, Wirtz, et al., 2010; Kaufmann, Schelling, Eisner, Richter, Krauseneck, Vogeser, et al., 2010). Experiments 2 and 3 employed a continuous measure of subjective sexual arousal, and used HLM to analyze the results, in order to further investigate the question of concordance between subjective and physiological sexual arousal.

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 to all three studies was that data were based on relatively small sample sizes. The sizes of the samples used in the current research are quite typical for sexual psychophysiology studies with women; however, the limited size of these samples, nonetheless, increases the risk of Type II errors and it is possible that significant associations between cannabinoids and sexual arousal were missed in this research due to this limitation. A second limitation is that Experiment 3 did not manipulate/investigate the effects of acute, dose- and potency-controlled cannabis consumption on sexual arousal. As such, no conclusions regarding the direct effects of marijuana use on sexual arousal were possible. In fact, given that Experiment 3 was correlational in nature, it cannot be ruled out that differences in physiological sexual arousal existed before women in the occasional user group began using marijuana. In other words, it is possible that women with diminished sexual arousal are more likely to use marijuana, perhaps in an effort to increase arousal. Third, this study did not examine the relationship between cannabinoids and either sexual desire and/or orgasm. Fourth, Experiments 1 and 2 used discrete sampling methods to measure endocannabinoid levels. As is the case when assessing the relationship between objective and subjective sexual arousal, sampling serum continuously, rather than discretely, would allow for a greater assessment of the exact relationship between sexual arousal and the endocannabinoid system. Finally, this research measured endocannabinoid levels in serum, as opposed to measuring endocannabinoid levels directly in the brain. Although serum levels likely reflect brain levels (given that endocannabinoids cross the blood-brain barrier) direct measurement of endocannabinoid levels in the brain would provide more specific information about the role of the endocannabinoid system in female sexual arousal than measurement of endocannabinoid levels in serum.

Much more research is needed to understand fully the role of the endocannabinoid system in female sexual arousal, and in female sexual function more generally. Nonetheless, the findings from this research provide exciting preliminary evidence that the endocannabinoid system has a role in female sexual arousal and contribute to knowledge regarding the physiology underlying female sexual functioning—an area which, to date, has remained poorly understood. Evidence that the endocannabinoid system plays an integral and direct role in female sexual functioning also has significant implications for the treatment of sexual dysfunctions. For example, if female sexual dysfunctions are found to be associated with either increased or decreased activity of this endogenous system, pharmacological treatments designed to activate or suppress this system have significant therapeutic potential. 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 can be anticipated. Given the findings of the current research, together with recent animal research which has shown a similar negative relationship between cannabinoids and sexual function (i.e., Ferrari et al., 2000; López et al., 2009, 2010), it is possible that cannabinoid antagonists/inverse agonists such as SR141716A (also known as rimonabant, and marketed under trade names such as Acomplia and Monaslim), which has been tested and prescribed in Europe as an anti-obesity agent due to its appetite suppressant effects, may also function as a pharmacological agent with beneficial effects on female sexual arousal. Approval for this drug was recently removed in Europe, and not granted in North America, due to concerns regarding possible psychiatric side effects (see Hill & Gorzalka, 2009); however, other possible pharmacological agents that similarly act on the endocannabinoid system are currently being investigated and, similarly, have potential to affect sexual function.

Although not in any way connected to the objectives of this research, understanding the role of the endocannabinoid system in sexual function also has implications for anti-drug campaigns. Should the endocannabinoid system be found to play an inhibitory role in sexual functioning in women, as is suggested by the current research, and if expectations regarding the role of cannabis on sexual function contribute to the etiology and/or maintainance of cannabis use, then the results of this and future research on this topic could be used, in part, as the basis for drug prevention programs.

The current research also contributes to the literature investigating whether physiological and subjective sexual arousal in women are one, unified construct, or whether physiological and subjective sexual arousal should be considered as conceptually distinct. Specifically, the current research validated findings by Rellini et al. (2005) that using a continuous measure of subjective sexual arousal, as opposed to non-continuous pre/post questionnaires that rely on retrospective recall, results in findings of significant concordance of subjective and physiological sexual arousal. As a result, past studies that found low or even no concordance between subjective and physiological sexual arousal may have been based on invalid approaches to measuring subjective sexual arousal. The implications of this are significant, in that much research and theory has gone into examining and suggesting explanations for this believed "desynchrony", or discordance, in women. In fact, the current research, together with the research by Rellini et al. (2005) suggests that proposals by experts in the field of human sexuality to distinguish between subjective and physiological sexual arousal when diagnosing female sexual arousal disorder, may not be warranted and that further research utilizing continuous measures of subjective sexual arousal is needed.

As alluded to, the current research points to a number of specific directions for future research. First, the findings of the current research need to be verified through replication, particularly given that Experiment 1 did not find a relationship between endocannabinoids and sexual arousal, while

Experiment 2 did. This discrepancy in findings is very likely due to the sample size and methodological limitations pertaining to Experiment 1, which were rectified in Experiment 2; however, given that one study found an effect while the other did not, additional, confirmatory research is warranted.

Second, it is hoped that future research will further the findings of Experiment 2 by examining endocannabinoid levels in relation to sexual arousal not only in sexually health women, but also in women with female sexual arousal disorder and other sexual dysfunctions. This will contribute to an understanding of the specific role (if any) of the endocannabinoid system in sexual difficulties. A particularly interesting study, relating to the question of concordance between subjective and physiological sexual arousal, would be to examine any differences in endocannabinoid levels between women who meet Basson and colleagues' criteria for genital FSAD versus women who meet the criteria for subjective FSAD (Basson, 2001, 2002a; Basson et al., 2000; 2003). Given that Experiment 2 found that levels of AEA were significantly related to both physiological and subjective sexual arousal, but that levels of 2-AG were found to be significantly related only to subjective sexual arousal, it is possible that differential effects of the two endocannabinoids on physiological versus subjective sexual arousal exist. If this were found to be the case, this would provide interesting evidence that subjective and physiological sexual arousal are, in fact, distinct concepts. At the same time, it must be recognized that the lack of a significant relationship between 2-AG and physiological sexual arousal in Experiment 2 may be due to Type II errors as a result of the relatively small sample size that was used.

Third, 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 than the findings of Experiment 3, which did not manipulate cannabinoid receptor activity directly and instead examined only the association between self-reported cannabis use and subjective and physiological sexual arousal.

The ethical constraints on administering cannabinoid agonists such as cannabis 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 line of 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.

Nonetheless, the findings from this research provide exciting preliminary evidence that the endocannabinoid system has a role in female sexual arousal. It is hoped that this research will stimulate further research in this area, and that the findings will increase understanding of biological bases underlying female sexual function. Ultimately, this understanding may lead to the development of effective pharmacological treatments for female sexual dysfunctions.

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