2010

HORMONAL MODULATION OF THE BEHAVIORAL EFFECTS OF TRAIZOLAM

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ABSTRACT OF DISSERTATION

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HORMONAL MODULATION OF THE BEHAVIORAL EFFECTS OF TRAIZOLAM

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfilment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By
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There is accumulating evidence from many directions indicating that gender plays a critical role in drug abuse. Biological factors, including gonadal sex hormones, contribute in a significant although incompletely understood manner, to gender differences in drug abuse. Female sex hormones have been shown to affect central nervous system function and modulate the effects of drugs of abuse. For example, $GABA_A$ receptor function is positively modulated by progesterone. There is evidence from preclinical in vitro and in vivo studies as well as some clinical research suggesting that progesterone and its metabolites may enhance the behavioral effects of benzodiazepines, which also serve as positive modulators of $GABA_A$ receptors.

The three studies presented here utilize within subject designs to assess the role of progesterone on the discriminative stimulus, subjective, performance and cardiovascular effects of triazolam, a short-acting benzodiazepine, in healthy, premenopausal women. The first study examined the effect of menstrual cycle phase on the discriminative stimulus effects of triazolam (0.00, 0.06, 0.12 and 0.25 mg/70 kg). The results of this study indicated that when progesterone levels peak (mid luteal phase), the discriminative stimulus effects of triazolam (0.12 mg/70 kg) are enhanced. The second study examined the separate and combined effects of a range of acute doses of oral micronized progesterone (0, 100 and 200 mg) and oral triazolam (0.00, 0.12 and 0.25 mg/70 kg) on the subjective, psychomotor and physiological effects of these medications, tested under conditions of low circulating sex hormones. The results of this study indicated that progesterone alone has some short-acting, sedative-like effects and enhances the subjective and performance effects of triazolam. The final study examined the effects of progesterone (0 and 100 mg) on the discriminative stimulus effects of triazolam (0.00, 0.06, 0.12 and 0.25 mg/70 kg), also under conditions of low circulating sex hormones. The results of this study indicated that the parent hormone progesterone does not appear to alter sensitivity to the discriminative stimulus effects of triazolam. Increases in sensitivity to triazolam in studies 1 and 2 may have been the result of neuroactive progesterone metabolites (e.g., allopregnanolone, TH-DOC), although future studies will be required to further examine this possibility. Taken together, these studies help clarify the manner in which the ovarian hormone progesterone and its metabolites modulate the behavioral effects of the benzodiazepines.

KEYWORDS: Progesterone, Neurosteroid, Benzodiazepine, Women's health, Drug Discrimination

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HORMONAL MODULATION OF THE BEHAVIORAL EFFECTS OF TRIAZOLAM

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CHAPTER 1

INTRODUCTION

BACKGROUND RESEARCH

There is increasing evidence that the functional effects of drugs differ among men and women. Greater numbers of men use and abuse illicit drugs than women (SAMHSA, 2009). However, there are marked differences between men and women in the relative risk of developing dependence on sedative-hypnotic drugs (e.g., benzodiazepines). After initiating sedative-hypnotic drug use, women are significantly more likely to develop problematic use patterns relative to their male counterparts, such that women may be nearly twice as likely to develop dependence on these compounds (Kandel et al., 1998; Anthony et al., 1994). In addition, women are prescribed sedative-hypnotic compounds at higher rates than men (Nomura et al., 2006; Howes et al., 1996; van der Waals et al., 1993; Wysowski & Baum, 1991), take the medications longer once prescribed (Geiselmann & Linden, 1991), and are more likely to use the medications for non-medical purposes (Simoni-Wastila et al., 2004).

Gender disparities are undoubtedly influenced by environmental variables (i.e., drug availability, socio-cultural variables); however, there is also evidence that gender differences may be biologically mediated, and perhaps influenced by ovarian hormones. Ovarian steroid hormones, such as estradiol and progesterone, crucial to peripheral nervous system function and reproductive health, modulate central nervous system (CNS) function. The non-genomic CNS actions of these steroids are mediated through neuronal receptor mechanisms, resulting in rather rapid modulation of the effects of psychoactive compounds. Although the neurosteroids progesterone and estradiol are present in men, the circulating blood levels are minimal and stable across time. The plasma levels of these hormones vary as a function of menstrual cycle phase and are present at different circulating levels in women. Since the receptor mechanisms modulated by steroid hormones overlap with those affected by drugs of abuse, it is critical to investigate whether ovarian hormones influence the abuse liability of drugs in women.

Although several sex hormones modulate drug action, a systematic examination of an individual ovarian hormone is an informative and productive approach, as it

provides detailed information regarding the relative influence of a single hormone in the acute effects of a drug. Therefore, the following series of studies focus on the effects of progesterone.

Progesterone and its primary metabolites, allopregnanolone, pregnanolone and TH-DOC, modulate neurotransmitter activity via both genomic and non-genomic mechanisms. The non-genomic effects of these neurosteroids include direct activation of neuronal membrane-bound receptors and the rapid modulation of several neurotransmitter systems including GABA, dopamine, opiate, glutamate and nicotinic acetylcholine systems (Pluchino et al., 2006; Lena et al., 1993). The most well-characterized and perhaps most influential, of progesterone's effects are those at the $GABA_A$ receptor complex. Sedative-hypnotic drugs such as the benzodiazepines also produce their effects, in large part, via modulation of $GABA_A$ receptors. Allopregnanolone, TH-DOC, and pregnanolone are ligands at extracellular, steroid-specific recognition sites on $GABA_A$ receptors, with affinities that are comparable to those of many benzodiazepines (Paul & Purdy, 1992; Majewska et al., 1986). In addition, these neurosteroids dose-dependently increase the effects of benzodiazepines on GABA-induced Cl^- currents, indicating that there is a receptor-level interaction between benzodiazepines and neurosteroids (Paul & Purdy 1992; Bertz et al., 1995). The behavioral effects of these neurosteroids also overlap with those engendered by benzodiazepines. Through $GABA_A$ modulation, neurosteroids can induce anxiolytic, sedative and antiepileptic effects (Schumacher et al., 1989).

The effects of progesterone and its metabolites on receptor function have been linked to many of the clinical effects of the hormone, including sedation, memory impairment, anxiolysis, depression, alcohol dependence, stress reduction and anti-seizure effects (Pisu & Serra, 2004; Rhodes et al., 2004; Schumacher & Robert, 2002; Rupprecht, 2003). Elucidation of the neuropharmacological effects of progesterone may elucidate some of the biological-mediated underpinnings of gender differences in these conditions.

Because progesterone metabolites have a direct action at GABA receptor sites, it is hypothesized that progesterone may potentiate the behavioral effects of GABAergic drugs. Preclinical studies have demonstrated such an effect. For example, Grant and colleagues have conducted research using non-human primates (Macaca fascicularis) and have demonstrated that the discriminative stimulus effects of ethanol are sensitive to menstrual cycle phase, such that the ethanol generalization curve is shifted to the left

during the mid-luteal phase of the menstrual cycle when progesterone levels surge (Grant et al., 1997, Green et al., 1999). In contrast, menstrual cycle mediation of the effects of GABAergic drugs in women has not been consistently reported. The reinforcing and subjective effects of ethanol have been examined across three phases of the menstrual cycle (early follicular, late follicular, luteal) in normally cycling, healthy women (Holdstock & de Wit, 2000). These investigators found no changes in alcohol effects as a function of menstrual cycle phase. The subjective and performance effects of triazolam have also been examined across three phases of the menstrual cycle (follicular, periovulatory, and luteal), with no menstrual cycle modulation reported (Rukstalis & de Wit, 1999). It remains to be seen whether procedures that have been developed to examine the receptor-mediated effects of drugs, such as the drug discrimination methodology (e.g., Kamien et al., 1993; Kelly et al., 2003; Colpaert, 1999) could be used to test the clinical neuropharmacology of progesterone in a more sensitive manner than has been possible using self-report and performance measures.

Sensitivity to the behavioral effects of benzodiazepines in women also may be more consistent when levels of neurosteroids are directly manipulated. When administered as a pre-treatment, exogenous oral micronized progesterone enhanced the sedative, memory and performance effects induced by oral triazolam in post-menopausal women (McAuley et al., 1995). In addition, women taking oral birth control containing both progesterone and estradiol were more sensitive to the performance impairing effects of alprazolam, lorazepam, and triazolam (Kroboth et al., 1985). Hormone pre-treatment studies have many methodological advantages over other approaches. When a hormone pre-treatment is administered when endogenous hormones are at nadir levels (e.g., the early follicular phase), it allows for the controlled examination of the effects of the hormone. In contrast, when drug effects are examined across the cycle, various hormone levels are in flux, making it difficult to apply a causal mechanism to a particular hormone. In addition, pre-treatment studies allow for multiple doses of hormone to be tested and dose-response relationships established. As such, it is clear that pre-treatment studies hold significant potential for examining the clinical neuropharmacology of progesterone and to elucidate potential gender differences in sensitivity to the effects of benzodiazepines.

The purpose of the following series of studies is to determine whether the ovarian hormone progesterone modulates the behavioral effects of the sedative drug triazolam using human laboratory methodologies. The first study will determine if elevated levels

of progesterone during the mid luteal phase of the menstrual cycle enhances the discriminative stimulus effects of triazolam, as compared to nadir levels of progesterone during the early follicular phase (i.e., menstrual cycle modulation of the discriminative stimulus effects of triazolam). The second study will examine the independent and combined subjective and psychomotor effects of exogenous progesterone and triazolam in healthy adult premenopausal women. The third study will examine whether exogenous progesterone pretreatment modulates the discriminative stimulus effects of triazolam.

RATIONALE

The purpose of Study 1 is to determine if the behavioral effects, including the discriminative stimulus effects, of triazolam are modulated as a function of menstrual cycle phase. Drug discrimination methodology is incorporated as a primary measure in this study because there is evidence that drug discrimination may be more sensitive to hormonal modulation and to the effects of drugs at the receptor level, than self-report measures alone (Lile et al., 2007; Kelly et al., 2003). It is hypothesized that the discriminative stimulus effects of triazolam will be enhanced during the mid-luteal phase, when progesterone levels are elevated, relative to the early follicular phase, when progesterone is at nadir levels. The results of this study will help elucidate the underpinnings of changes in acute drug effects across the menstrual cycle. However, given that several hormonal changes occur across the menstrual cycle, it is not possible to determine from these results if a specific hormone modulates the effect of triazolam. Instead, these results will provide indirect information about the relationship between the hormonal array present during specific phases of the menstrual cycle and the behavioral effects of triazolam. Specifically, this study will not reveal if the potentiation of the discriminative stimulus effects of triazolam during the mid-luteal phase reflects independent or combined effects of progesterone or estradiol modulation of benzodiazepine effects, since both steroids are elevated during the mid-luteal phase. Similarly, it will not be possible to determine whether menstrual cycle effects are associated with acute or repeated exposure to elevated hormones. Thus, it is necessary to conduct pre-treatment studies to isolate and manipulate the effects of progesterone to determine if the changes in triazolam effects during the mid-luteal phase are due specifically to the acute presence of progesterone.

The purpose of Study 2 is to test the behavioral effects of several dose

combinations of both oral progesterone and triazolam. This study will examine the separate and combined behavioral effects of progesterone and triazolam across a range of doses in order to evaluate the interactive effects of these two compounds. As this is the first study to examine the independent and combined effects of these two medications, it is important to establish dose-response relationships. Clinically relevant doses of progesterone and triazolam are tested in that the progesterone doses will engender progesterone plasma levels that are consistent with those naturally occurring across the menstrual cycle (Chakmakjian & Zachariah, 1987; Sofuoglu et al., 2001; de Wit et al., 2001; Soderpalm et. al., 2004), and the triazolam doses are within the dose range recommended for therapeutics (Physician's Desk Reference, 2006). This study will extend the results of the first study by directly examining the effects of physiological doses of progesterone, alone and in combination with a dose range of triazolam. It is hypothesized that progesterone will potentiate the effects of triazolam.

The purpose of Study 3 is to utilize drug discrimination methodology to more precisely examine the neuropharmacological effects of progesterone, alone and combination with triazolam, as drug discrimination has been shown to be an effective tool in examining pharmacological changes mediated by receptor-based interactions (Colpaert, 1999; Kelly et al., 2003). The results of Study 2 will inform the pretreatment dose of progesterone to be used in Study 3. It is hypothesized that progesterone pretreatment will potentiate the discriminative stimulus, and other behavioral effects of triazolam.

IMPLICATIONS

Overall, understanding the mechanisms by which neurosteroids modulate neurotransmitters systems has important clinical implications. Neurosteroids, specifically progesterone metabolites, modulate several behaviors and disease conditions, as variations in these hormones contribute to predisposing or protecting individuals from sleep disturbances, anxiety, depression, epilepsy, dementia, and post-partum depression (Bicikova et al., 2000, Ströhle et al., 2003; Romeo et al., 1993; Murialdo et al., 2001; McCoy et al., 2003; Rupprecht, 2003). Not only are these hormones a factor in individual differences in disease processes, variation in neurosteroid levels also contributes to individual differences in drug effects. For example, levels of endogenous progesterone metabolites have been correlated with the severity of ethanol tolerance and withdrawal, and the efficacy of anxiolytic medications

(Romeo et al., 1996; 2000; Le Mellédo et al., 2000; Brambilla et al., 2005; Ho et al., 2004). As hormones rapidly fluctuate across the menstrual cycle, intra-individual differences in hormonal modulated drug effects are particularly evident in women. For example, hormonal changes across the cycle can often necessitate modifications in doses of anti-epileptics (Reddy, 2009; Herzog et al., 2009; Bäckström, 1976) and anesthetics (Erden et al., 2005) to properly maintain the condition without adverse side effects. As such, understanding the role of neurosteroids in drug modulation may lead to a greater understanding of gender and individual differences in the effects of certain drugs. Taken together, elucidating the biological underpinnings of the gender differential observed in abuse and dependence liability may inform gender-specific drug prevention and treatment strategies.

CHAPTER 2

STUDY 1: Modulation of the discriminative stimulus effects of triazolam across the menstrual cycle phase in healthy pre-menopausal women

INTRODUCTION

Progesterone is a positive modulator of the $GABA_A$ receptor complex, and its primary metabolites allopregnanolone, pregnanolone and TH-DOC function as ligands at extracellular steroid-specific recognition sites on $GABA_A$ receptors with affinities that are comparable to those of many benzodiazepines (Bertz et al., 1995; Paul & Purdy, 1992; Majewska, 1992; Majewska et al., 1986). Through $GABA_A$ modulation, progesterone induces behavioral effects similar to those engendered by benzodiazepines (e.g., anxiolysis, sedation and antiepileptic effects) (Frye, 2007; Rupprecht, 2003; Schumacher et al., 1989), and changes in progesterone levels across the menstrual cycle have been shown to modulate the behavioral effects of GABAergic drugs in pre-clinical models. Grant and colleagues, for example, demonstrated that sensitivity to the discriminative-stimulus effects of alcohol was enhanced in non-human primates during the mid-luteal phase of the menstrual cycle when progesterone levels are elevated compared to the follicular phase when progesterone levels are minimal (Grant et al., 1997, Green et al., 1999). In contrast, few changes in the reinforcing or subjective effects of ethanol or triazolam have been reported across the menstrual cycle in normally cycling, healthy women (Holdstock & de Wit, 2000; Rukstalis & de Wit, 1999). Inconsistencies in menstrual cycle phase modulation of sedative drug effects across studies could be related to differences in either species or methods used to assess drug effects. The current study addressed these inconsistencies by examining the discriminative stimulus effects of triazolam during the mid-luteal and early follicular phases of the menstrual cycle in normally cycling, healthy women. It was hypothesized that the discriminative stimulus effects of triazolam would be enhanced during the mid-luteal phase.

METHOD

Participants

Healthy pre-menopausal women were recruited through local newspaper advertisements and with flyers posted on a university campus. All potential participants completed an initial telephone or internet-based screening questionnaire, and an on-site medical evaluation that included a menstrual history, health questionnaires, blood chemistry and urinalysis. Eligibility criteria included a minimum of 18 years of age, good health, reports of intermittent sedative drug use (e.g., alcohol) and regular menstrual cycles (monitored across two menstrual cycle phases prior to participation). Exclusion criteria included significant medical history (e.g., cardiovascular, neurological, or major psychiatric illnesses, including drug or alcohol dependence), regular use of drugs or alcohol, other than nicotine or caffeine, use of hormonally-based contraceptives, pregnant or breastfeeding status, or any other condition that for which triazolam administration would be contraindicated.

Twenty participants met eligibility criteria and initiated the study. Eight participants withdrew from the study for reasons unrelated to the study protocol, five were discontinued from the study because they did not acquire the drug discrimination; data from these thirteen participants were excluded from analyses. Table 1.1 details demographic variables of participants who were unable to acquire the discrimination and the participants who successfully acquired the discrimination. None of the variables examined were consistently related to acquisition (either successful or unsuccessful) of the discrimination. Seven volunteers completed the study. The participants ranged in age from 21 to 43 years (median = 30 years), in weight from 47 to 69 kg (median = 60 kg), and drank 1 to 6 alcohol drinks per month (median = 2). One participant was a smoker (mean of 10 cigarettes per day); however, she abstained from smoking for the duration of each session.

Design

A double-blind, placebo-controlled, randomized within-subject design was used to assess the effects of menstrual cycle phase (early follicular and mid luteal), triazolam dose (training doses: 0.0, and 0.25 mg/70 kg, test doses: 0.06, 0.12 mg/70 kg), and time (assessments occurring pre-dose, 30, 60, 90, 120 and 150 minutes post-dose) on the

discriminative stimulus and other behavioral effects of triazolam.

Participants were instructed to abstain from alcohol and all medications for 24 hours and caffeine and food for 4 hours prior to their scheduled sessions. At the beginning of each session, participants were asked questions about medication use, sleep, food consumption and health status for the preceding 24 hours. No sessions were cancelled due to reports of atypical activities. Participants then completed a field-sobriety test, provided a breath sample that was tested for alcohol use (Alco-Sensor III, Intoximeters, Inc., St. Louis, MO) and provided a urine sample that was tested for amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, MDMA, and opiates (E-Z Split Key Cup, ACON Laboratories, San Diego) and pregnancy (hCG One Step Pregnancy Test Device, Instant Technologies, Inc., Norfolk, VA).

Assessments used to measure drug effects included a Drug Discrimination Task (post-dose only), Visual Analog (VAS) and Adjective Rating (ARS) Scales, Digit Symbol Substitution Task (DSST), and heart rate and blood pressure measurement (Sentry II, NBS Medical, Costa Mesa, CA).

Drugs

Doses of triazolam were prepared by the University of Kentucky Investigational Pharmacy. Triazolam (0.00, 0.06, 0.12 and 0.25 mg/70 kg) was prepared in size 0 opaque capsules, with cornstarch filler. Placebo capsules contained only cornstarch filler. Triazolam doses were delivered orally.

Assessment Tasks

Drug-Discrimination Task

During this task, two circles labeled with a color code (i.e., “Red” and “Blue”) were displayed on the computer screen, each associated with a training dose condition. Counters were displayed directly below the circles. A mouse controlled the location of a cursor on the screen, and mouse button presses with a cursor positioned on a circle increased the counter associated with that circle according to a fixed-interval 1-sec schedule. The cursor could alternate across the circles without any consequence under the fixed-interval schedule (i.e., no change-over-delay). Up to 60 points could be allocated across the two options. The dependent variable for this task was the percent

responding on the active drug-appropriate option.

Drug discrimination procedure

Sampling Phase

The sampling phase consisted of four sessions; each of the triazolam training doses (0.00 and 0.25 mg/70 kg) was administered on two sessions in an alternating pattern. For every participant, the training doses were associated with a fixed color code throughout the study, with the color-dose combinations and order of presentation being randomized across participants. Dose color was identified during drug administration, and participants were told to associate the effects of the dose with that color. Sampling sessions were conducted without regard to menstrual cycle phase.

Control Phase

Training doses of triazolam (0.00, 0.25 mg/70 kg) were administered randomly under double-blind conditions, and participants were not told which dose was administered until after the last assessment of a session. Acquisition of drug discrimination was established when ≥ 80% of responses were allocated to the drug-appropriate stimulus during the last assessment of the session (150 minutes post-dose) for 5 consecutive sessions. If the acquisition criterion was not met within 15 sessions, participation ended. Participants who met criteria did so within 5 to 15 sessions. Control sessions were conducted without regard to menstrual cycle phase and occurred immediately following training sessions.

Test Phase

Test Phase sessions were identical to control sessions, except that both training and test (0.06 and 0.12 mg/70 kg) doses were presented, and sessions were scheduled only during specific phases of the menstrual cycle. Participants completed 6 sessions during the early follicular phase of the menstrual cycle (days 1-7 following onset of menses) and 6 sessions during the mid-luteal phase of their menstrual cycle (days 5-12 following ovulation, as determined using daily urine assessments). During each cycle phase, each training dose was administered once and each test dose was administered twice. The order of menstrual cycle phase testing (i.e., whether test sessions began during the early follicular or mid-luteal phase) was randomized and varied among

participants. Sessions were scheduled around participants' availability within each menstrual cycle phase. Because time during any particular cycle phase was limited, participants completed the Test Phase across two or three consecutive cycle phases (i.e., across several months), such that some sessions were consecutive while others were separated by days or weeks. The length of time that elapsed between Control and Test Phase sessions varied depending on when participants' next cycle phase occurred and ranged from zero days to three weeks.

After the final assessment on every session, participants were told whether a red dose, a blue dose, or a test dose had been administered. On red and blue dose (i.e., training) sessions, participants received $0.04 per point accumulated on the circle associated with the dose administered on that session. On test dose sessions, participants received the average of earnings on training dose sessions, regardless of point distributions.

VAS

Participants 9 rated items presented individually on the computer by marking a 100-unit line anchored on the extremes by "Not At All" and "Extremely". Items included were: Stimulated, Sedated, Anxious, High, Confident, Hungry, Thirsty, Drug Effect, and Like Drug Effect.

ARS

The Adjective Rating Scale consists of 32 items and contains two subscales: Sedative and Stimulant (Oliveto et al., 1992). Participants rated each item using a numeric keypad to select one of five options: "Not at All", "A Little Bit", "Moderately", "Quite A Bit" and "Extremely" (scored numerically from 0 to 4, respectively; maximum score =64).

DSST

Participants completed a 2 minute computerized version of the DSST adopted from McLeod et al., 1982. The dependent measures for this psychomotor task were trial completion rate and accuracy.

Data Analysis

Triazolam effects were analyzed using repeated-measures ANOVA with triazolam dose, menstrual cycle phase and time as factors. Interactions were evaluated using simple-effects analyses.

RESULTS

Drug Discrimination Task

Figure 1.1 presents mean drug-appropriate responding as a function of triazolam dose administration during control and test sessions. During the final 5 control sessions, which occurred at different menstrual cycle phases across subjects, drug-appropriate responding emerged only after the active dose of triazolam was administered [dose by time interaction: $F(4, 24) = 14.78$, $p < .001$], and greater than 80% responding occurred reliably on the drug-appropriate option for all subjects beginning at 90 minutes post dose. During the test phase, active drug-appropriate responding varied as a function of menstrual cycle phase [dose x phase interaction: $F(12, 72) = 2.13$, $p = .025$], with simple effects analysis indicating significant cycle phase effects occurring at the 0.12 mg/70 kg test dose [$F(9, 27) = 7.90$, $p < .001$]. During the early follicular phase, three of seven subjects identified placebo as triazolam, resulting in intermediate levels of responding when averaged across all subjects, but responding was not significantly different from that occurring during the mid-luteal phase at this dose. The 0.06 mg/70 kg dose was identified as placebo during both cycle phases. The 0.12 mg/70 kg test dose was identified as triazolam-like during the mid-luteal phase, whereas during the early follicular phase, responding was comparable to that observed following placebo administration. The active training dose of triazolam (0.25 mg/70 kg) engendered triazolam-appropriate responding during both menstrual cycle phases.

Adjective Rating Scale

A dose by menstrual cycle phase interaction was detected on the Stimulant subscale of the ARS ($p \leq .05$), with ratings at the 0.06 mg/70 kg dose showing greater decreases during the mid-luteal phase relative to the early follicular phase (simple effects: $p \leq .05$).

Other Measures

Consistent with previous studies (e.g., Rush et al., 2000; 1999; Stoops et al., 2005), triazolam engendered prototypical sedative effects on many self-report, performance, and cardiovascular measures (Table 1.2). Baseline cardiovascular measures varied across cycle phases (e.g., Ounis-Skali et al., 2006), but triazolam effects were independent of cycle phase across all other measures.

Additional data (means and standard errors for each measure collected) are available in Appendix A.

DISCUSSION

The results of this study clearly demonstrate that triazolam functioned as a discriminative stimulus in healthy women and that sensitivity to the discriminative stimulus effects of triazolam was influenced by menstrual cycle phase. The discriminative stimulus effects of the 0.12 mg/70 kg test dose were enhanced during the mid-luteal phase, compared to the early follicular phase, of the menstrual cycle. These results, along with a growing body of literature, support the hypothesis that progesterone modulates the behavioral effects of GABAergic drugs (e.g., Grant et al., 1997, Green et al., 1999; Kroboth et al., 1985; McAuley et al., 1995).

Menstrual cycle phase effects were detected with drug discrimination and with the stimulant subscale of the ARS. Previous research using drug discrimination with nonhuman primates showed enhanced sensitivity to alcohol effects during the mid-luteal phase (Grant et al., 1997, Green et al., 1999); however, self-report measures of sedative drug effects have not typically changed across menstrual cycle phases in clinical studies (e.g., Holdstock & de Wit, 2000; Rukstalis & de Wit, 1999). These data suggest that drug discrimination may be more sensitive to menstrual cycle phase modulation of sedative drug effects than self-report measures alone. It is has been suggested that drug discrimination may be more sensitive to drug action at the receptor level, such that drugs with similar pharmacological profiles share similar discriminative effects, while subjective effect measures may be more likely to reflect interoceptive cues engendered by non-pharmacological states (Kelly et al., 2003). As drug discrimination establishes consistent

responding in the presence of a drug effects, it provides formalized pharmacological training for each participant, whereas subjective measures rely on participants' verbal history to identify interoceptive drug effects. The discordance between the discriminative stimulus and subjective effects of drugs has been reported across several drug classes (Preston & Bigelow, 1991; Chait et al., 1986; Kelly et al., 2003) and may be in part influenced by verbal conditioning history, contingencies associated with responding, or training conditions.

During control sessions, which were scheduled without regard to menstrual cycle phase, the 0 mg/70 kg dose engendered consistent responding on the non-drug option. Surprisingly, during the early follicular phase of test sessions, placebo engendered triazolam-appropriate responding in three of seven participants. The potential influence of several factors was examined, including the number of days post menses of testing, prior drug use history, rate of acquisition of the triazolam discrimination, and menstrual cycle phase during control sessions, but none served as a reliable predictor of placebo responding during the early follicular phase.

There were a few notable limitations to the current study. First, although cycle phases were determined using the onset of menses and objective measures of ovulation among women with regular menstrual cycles, plasma hormone levels were not measured. The correlations between serum levels of estradiol and progesterone and drug response have been demonstrated (White et al, 2002; Justice & de Wit, 2000; de Wit & Rukstalis, 1997). Second, the Sampling and Control Phases of the discrimination training were conducted without regard to menstrual cycle phase. It is possible that varied hormone levels during sampling and control phases may have influenced either rate of acquisition of the discrimination or results obtained during the test phase. However, we were unable to identify any factors, related to cycle phase or otherwise, that were associated with individual differences in the rate of acquisition of the discrimination. Furthermore, the proportion of participants acquiring the drug discrimination (7 of 12) is comparable to that in other triazolam drug discrimination studies (Vansickle & Rush, 2006; Rush et al., 2003; Rush et al., 2000; Kamien et al., 1997). Third, although a within-subject design was employed, the sample size was modest, and the sensitivity of self-report and other measures to cycle phase effects might have been established with a larger sample.

Although this study provided clear evidence that the effects of triazolam vary across the menstrual cycle, the relative role of progesterone in this effect is unclear. During the early follicular phase, both progesterone and estrogen are at nadir levels. During the mid luteal phase, peak levels of progesterone emerge; however, estrogen levels are elevated as well. Despite the well-documented evidence of progesterone and its metabolites modulating $GABA_A$ activity through a receptor-based mechanism, this study cannot provide conclusive evidence that the interaction observed was exclusively mediated by elevated levels of endogenous progesterone. Therefore, follow-up studies were conducted to isolate and directly manipulate the effects of progesterone to determine if acute progesterone administration modulates the effects of triazolam.

Table 1.1. Demographic data from participants who acquired the triazolam discrimination and those who were unable to acquire the discrimination.

	Discriminators (*n*=7)	Non-Discriminators (*n*=5)
Age	29.86	20.20
Weight (kg)	59.71	70.00
Caffeine (mg/day)	105.58	29.33
Alcohol (drinks/week)	0.53	2.30
Nicotine (cigarettes/day)	10 (*n*=1)	0.17 (*n*=1)
Other drug use	None reported	None reported
Beck	4.29	2.00
MAST	1.29	3.40
ADHD	2.57	3.40

Table 1.2. Significant F-values of selected measures for which a significant main effect or interaction was obtained. No Triazolam x Cycle x Time interactions were detected.

	Triazolam	Cycle	Triazolam x Cycle	Triazolam x Time	Cycle x Time
Self-Report Measures					
VAS					
Sedated	4.51			2.87	
High	3.19			2.03	
Drug Effect	4.35			3.94	
Hungry					2.75
Like Drug Effect				1.84	
ARS					
Sedative	6.67			4.37	
Stimulant			4.16		
Performance Measures					
DSST					
Trial Rate	4.62			2.25	
Proportion Correct					
Cardiovascular Measures					
Heart Rate	3.49	36.54		2.16	
Systolic					
Diastolic	4.45	7.09			4.00

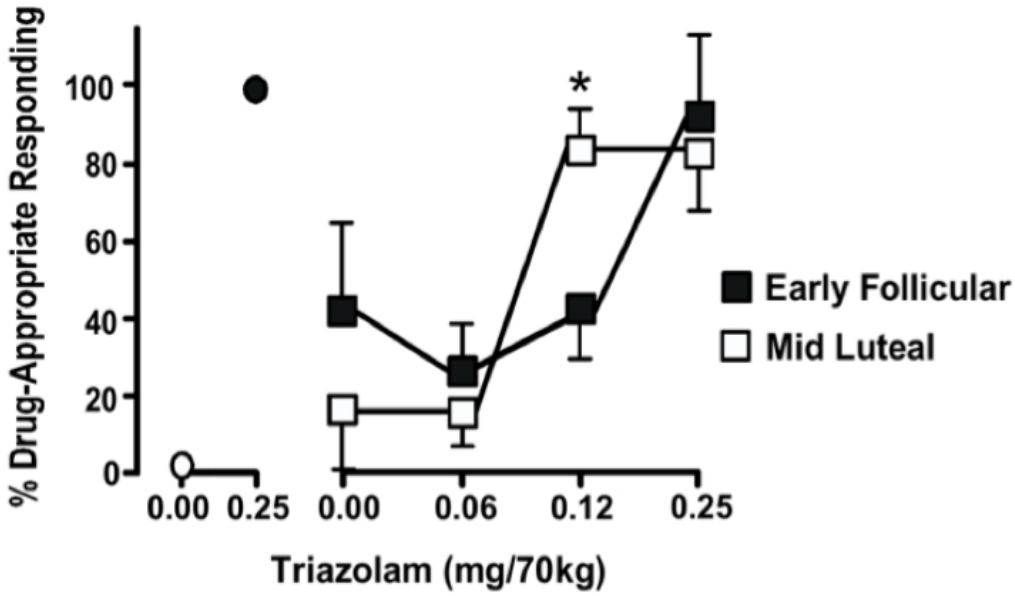

FIGURE 1.1. Average triazolam-appropriate responding as a function of triazolam dose and menstrual cycle phase from assessments occurring between 90 and 150 minutes post dose. The left panel displays responding during the Control Phase, during which training doses were administered. Data points represent means (± SEM denoted by the error bars) of seven subjects. The asterisk indicates a significant difference ($p \leq .05$) across cycle phase.

CHAPTER 3

STUDY 2: Separate and combined effects of progesterone and triazolam in healthy, premenopausal women

INTRODUCTION

Gender differences in drug use and abuse are notable, with greater numbers of men reporting non-medical use of drugs than women (SAMHSA, 2009). However, the relative risk of developing dependence on sedative-hypnotic drugs (e.g., benzodiazepines) appears to be greater for women than men. After initiating sedative-hypnotic drug use, women are significantly more likely to develop problematic use patterns relative to their male counterparts, such that women may be nearly twice as likely to develop dependence on these compounds (Kandel et al., 1998; Anthony et al., 1994). In addition, women are prescribed sedative-hypnotic compounds at higher rates than men (Nomura et al., 2006; Howes et al., 1996; van der Waals et al., 1993; Wysowski & Baum, 1991), take the medications longer once prescribed (Geiselmann & Linden, 1991), and are more likely to use the medications for non-medical purposes (Simoni-Wastila et al., 2004).

Biological factors, including ovarian hormones, and more specifically the neurosteroid progesterone and its metabolites, might contribute to these gender differences in sedative-hypnotic drug abuse. Neurosteroids (e.g., progesterone, estradiol) are abundantly present in premenopausal women, with plasma concentrations varying as a function of menstrual cycle phase. Research from a variety of sources indicates that neurosteroids modulate receptor systems and alter drug effects (McAuley et al., 1995; White et al., 2002; Justice et al., 1999; Lynch et al., 2002; Lile et al., 2007). Progesterone and its primary and derivative metabolites, allopregnanolone, pregnanolone, and TH-DOC, modulate neurotransmitter activity via genomic and non-genomic mechanisms. The non-genomic effects of these neurosteroids include direct activation of neuronal membrane-bound receptors and the rapid modulation of several neurotransmitter systems including GABA, dopamine, opiate, glutamate and nicotinic acetylcholine systems (Pluchino et al., 2006; Lena et al., 1993). The best-characterized and perhaps most influential of progesterone's effects are those at the $GABA_A$ receptor complex. Sedative-hypnotic drugs such as the benzodiazepines also produce their

effects, in large part, via modulation of $GABA_A$ receptors. Allopregnanolone, pregnanolone and TH-DOC are ligands at extracellular, steroid-specific recognition sites on $GABA_A$ receptors, with affinities that are comparable to those of many benzodiazepines (Paul & Purdy, 1992). In addition, these neurosteroids dose-dependently increase the effects of benzodiazepines on GABA-induced Cl^- currents, indicating that there is a non-genomic, receptor-level interaction between benzodiazepines and neurosteroids (Paul & Purdy, 1992; Bertz et al., 1995). The behavioral effects of these neurosteroids also overlap with those engendered by benzodiazepines and include sedation, memory impairment, anxiolysis, depression, stress reduction and anti-seizure effects (Pisu & Serra, 2004; Rhodes et al., 2004; Rupprecht, 2003; Schumacher et al., 1989; Schumacher & Robert, 2002).

Because progesterone and its metabolites have a direct action at GABA receptor sites, it is hypothesized that progesterone may potentiate the behavioral effects of GABAergic drugs. Preclinical studies have demonstrated that the discriminative stimulus effects of ethanol are sensitive to menstrual cycle phase, such that the ethanol generalization curve is shifted to the left during the mid-luteal phase of the menstrual cycle when progesterone levels surge (Grant et al., 1997, Green et al., 1999). Similar effects were observed in healthy, pre-menopausal women in Study 1, such that the discriminative stimulus effects of triazolam were potentiated during the mid-luteal phase relative to the early follicular phase. Other clinical research examining GABAergic drug effects (i.e., triazolam and ethanol) across the menstrual cycle have found little or no evidence for cycle modulation of drug effects (Holdstock & de Wit, 2000; Rukstalis & de Wit, 1999).

Interactions between neurosteroids and benzodiazepines may be more apparent when levels of neurosteroids are directly manipulated. Examining drug effects across the menstrual cycle does not allow for a direct assessment of the effects of progesterone because progesterone level increases during the mid-luteal phase coincide with estradiol level increases. An alternative strategy is to assess the effects of exogenously administered progesterone during the early follicular phase when both progesterone and estradiol levels are at nadir levels. When administered as a pre-treatment, exogenous oral micronized progesterone enhanced the sedative, memory-impairing and performance effects induced by intravenous triazolam in post-menopausal women (McAuley et al., 1995). Those results support the use of this methodology to more

directly examine interactions between neurosteroids and drug effects. However, there do not appear to be any studies that used progesterone-only pretreatments to evaluate potential interactions between neurosteroids and sedative-hypnotic drugs in healthy pre-menopausal women, who might be at increased risk for developing benzodiazepine-use disorders. Thus, further study of the effects of GABAergic drugs following controlled administration of progesterone is warranted and should not only provide additional useful information regarding progesterone modulation of the GABA-mediated behavioral effects of drugs, but also help elucidate gender-specific sensitivity to the effects of benzodiazepines. The purpose of the present study is to determine the independent and combined subjective and psychomotor effects of progesterone and triazolam in healthy adult premenopausal women.

METHOD

Participants

This study used methods similar to those of Study 1 and participant recruitment procedures, medical screening protocol and exclusion criteria were the same across studies. Eligibility criteria for this study was slightly different and included a minimum of 18 years of age, reports of occasional sedative drug use (e.g., alcohol), and use of an oral, hormone-based contraceptive that included a 7 consecutive-day placebo phase.

Sixteen participants were enrolled in the study. Five participants did not complete the study for reasons unrelated to the protocol and their data are not included in the analyses. Eleven women (10 Caucasian, 1 African American) completed the study. The participants ranged in age from 21 to 26 years (median = 22 years) and in weight from 51 to 72.4 kilograms (median = 63 kg; BMI range= 19.2 to 26.3, median = 22.2). All participants were non-smokers. Alcohol use ranged from less than 1 to 7.5 alcohol drinks per week (median = 3) and caffeine use ranged from 0 to 185 mg of caffeine per day (median = 80 mg). One participant reported nonmedical use of a prescription stimulant medication (i.e., Adderall) on two occasions in the month prior to study participation. Participants reported no additional psychoactive drug use in the month prior to study participation and no drug use was detected during the study with daily urinalysis testing. Participants were compensated for their participation.

Design

A double-blind, placebo-controlled, randomized design was used to assess the effects of three within-subject variables, progesterone dose (0, 100 and 200 mg), triazolam dose (0.00, 0.12 and 0.25 mg/70 kg), and time (30, 60, 90, 120 and minutes after triazolam administration, which correspond to 75, 105, 135, 165, 195 after progesterone administration), on the subjective, performance and cardiovascular effects of triazolam during the early follicular phase of the menstrual cycle (e.g., the placebo phase of the oral birth control regimen) when estrogen and progesterone levels are at their nadir.

Drugs

Doses of progesterone and triazolam were prepared by the University of Kentucky Investigational Pharmacy. Progesterone (0, 100, 200 mg; Prometrium) and triazolam (0.00, 0.12 and 0.25 mg/70 kg) were prepared in size 00 and 0 distinct opaque capsules, respectively, each with cornstarch filler. Placebo capsules contained only cornstarch filler. Both progesterone and triazolam doses were delivered orally.

Schedule

Participants completed one training session prior to the experimental sessions to acquaint them with the study procedures and to establish consistent and accurate performance on computerized behavioral tasks. This practice session was conducted irrespective of menstrual cycle phase but within one week of the initiation of the experimental sessions. The subsequent nine experimental sessions were conducted during the participant's placebo phase of their oral birth control regimen (e.g., early follicular phase). Each permutation of progesterone and triazolam doses was tested once in random order. Each experimental session was 6 hours in length. Participants completed the study across 2-4 months time, with each session occurring at approximately the same time of day across the study.

Screening and laboratory check in procedures (i.e., drug testing, field sobriety test) were identical to those used in Study 1 and were consistent across studies.

Thirty minutes after progesterone administration, participants consumed a moderate-fat snack to enhance progesterone absorption (Simon et al., 1993; Stanczyk, 1999). Triazolam was administered 15 minutes after snack delivery. Assessments were repeated in 30-minute intervals for 3 hours after triazolam administration. Each

assessment consisted of Visual Analog (VAS) and Adjective Rating (ARS) Scales, Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS), Digit Symbol Substitution Task (DSST), Balloon Analog Risk Task (BART) and heart rate and blood pressure measurement (Sentry II, NBS Medical, Costa Mesa, CA). Only measures that are different form those used in Study 1 are described below.

Assessment Tasks

VAS

Similar to the version used in Study 1, the scale presented in the current study included 32 items, including: Stimulated, Stressed, Sedated, Anxious, Nervous, Light-Headed, Sleepy, Sick to Stomach, Shaky, Jittery, Depressed, High, Euphoric, Active, Alert, Energetic, Drug Effect, Good Drug Effect, Bad Drug Effect, Performance Impaired, Performance Improved, Like Drug, and Pay for Drug.

ARCI

The 49-item short form of the true-false inventory (Martin et al., 1971) yielded information on five dimensions: Lysergic Acid Diethylamide (LSD) scale, Amphetamine (A) Scale, Benzedrine-Group (BG) Scale, Morphine-Benzedrine Group (MBG) Scale and the Pentobarbital, Chlorapromazine, Alcohol Group (PCAG) Scale.

ARS

The Adjective Rating Scale consists of 32 items and contains two subscales: Sedative and Stimulant (Oliveto et al., 1992). In the present study, only the 16 items from the Sedative subscale were presented. Participants rated each item using a numeric keypad to select one of five options: “Not at All”, “A Little Bit”, “Moderately”, “Quite A Bit” and “Extremely” (scored numerically from 0 to 4, respectively; maximum score =64).

BART

Participants were presented with 20 individual balloons in succession on a computer screen, as adapted from Lejuez et al., 2002. Participants clicked a mouse to inflate each balloon. Each inflation increased the balloon earnings counter by $0.01 and increased the probability of the next inflation to pop the balloon. Each balloon would pop

after a random, unpredictable number of inflations. Participants could collect their balloon earnings prior to a balloon popping by clicking on a "Collect Money" option. However, if a balloon popped, earnings from the balloon were permanently lost. Earnings from each task presentation were recorded and participants were given their task earnings from a randomly chosen assessment at the end of the session. The dependent measures were number of inflation responses per un-popped balloons, and number of balloons popped.

Data Analysis

Drug effects were analyzed using repeated-measures ANCOVA with progesterone dose, triazolam dose and time as factors and baseline assessment prior to drug administration serving as a covariate. Significant interactions were evaluated using simple-effects analyses. Because baseline measures were used as covariates, drug effects were identified by a main effect of dose or a dose by time interaction, depending on the time course of the drug effect. Similarly, drug interactions were apparent as either a drug by drug interaction, or a drug by drug by time interaction, again depending on the time course of the interaction.

RESULTS

Independent of progesterone, triazolam produced prototypical sedative-like effects on multiple measures including VAS Sleepy, ARS Sedated and POMS Fatigue (Table 2.1). Figure 2.1 presents VAS ratings of Drug Effect (top row), VAS ratings of Sedated (middle row) and ARCI PCAG Scale ratings (bottom row) as exemplars. Triazolam increased subjective ratings on each scale, as evidenced by a main effect of triazolam and triazolam by time interaction (Table 2.1). Based on simple effects analyses, triazolam effects occurred at the high dose of triazolam (0.25 mg/70 kg) 90 through 150 minutes after dose administration on VAS Drug Effect (Figure 2.1, open squares, panels A through C) and ARCI PCAG scale (open squares, panels D through F), and occurred 120 through 150 minutes on the VAS Sedated Scale (open squares, panels G through I).

Both doses of progesterone also produced sedative-like effects on a profile of measures similar to those of triazolam (Table 2.1). Figure 2.1 (left column) displays the time course of progesterone alone on VAS Drug Effect (panel A), VAS Sedated (panel D), and ARCI PCAG scale (panel G), with peak effects of progesterone in combination

with placebo triazolam occurring 75 through 105 minutes after progesterone administration (i.e., 30 through 60 minutes post triazolam administration).

A significant interaction between progesterone and triazolam was also detected on the sedative-like measures of drug effect, including POMS Fatigue (Table 2.1). Figure 2.1 (top row) displays the progesterone by triazolam interaction on ratings of VAS Drug Effect. Simple effects analysis indicated significant progesterone effects at all doses of triazolam, with increases occurring at both active doses of progesterone in combination with the moderate dose (0.12 mg/70 kg) of triazolam (panel B) and increases occurring at 200 mg of progesterone in combination with the high dose (0.25 mg/70 kg) of triazolam (panel C) ($p < .05$). Compared to progesterone alone (panel A), the combination of progesterone and triazolam extended the duration of and delayed peak ratings of VAS Drug Effect (panels B and C). Significant interactions were not detected on ratings of VAS Sedated and ARCI PCAG, but the profile of effects were similar to those of VAS Drug Effect, with increases in occurring when either dose of progesterone was combined with the moderate dose of triazolam (0.12 mg/70 kg) (panels E and H) and when 200 mg was combined with the high dose of triazolam (0.25 mg/70 kg) (panels F and I), the peak effects were delayed. .

Separate and combined effects of progesterone and triazolam were also observed on measures that have typically considered to be indirect measures of the reinforcing and aversive effects of drugs. For example, independent of progesterone, triazolam increased ratings of VAS Euphoric and High (Table 2.1). Figure 2.2 displays ratings of VAS Good Drug Effect (top row), VAS Bad Drug Effect (middle row) and VAS Pay for Drug (bottom row) as representative measures. Triazolam modified ratings on each scale, as evidenced by a main effect of triazolam (Table 2.1). The high dose of triazolam (0.25 mg/70 kg) increased ratings of VAS Good Drug Effect (Figure 2.2, open squares, panels A through C) and VAS Bad Drug Effect (open squares, panels D through F), and decreased ratings of VAS Pay For Drug (open squares, panels G through I), with these effects occurring at 90 through 150 minutes after triazolam administration.

As evidenced by a main effect of progesterone (Table 2.1), progesterone alone also increased ratings of VAS Good Drug Effect 75 through 105 minutes after progesterone administration (Figure 2.2, panel A) and VAS Bad Drug Effect at 105 to 135 minutes (panel D). No main effect of progesterone was detected on VAS Pay for

Drug (panel G).

A significant interaction between progesterone and triazolam was detected on each measure presented in Figure 2.2. Simple effects analyses of ratings of VAS Good Drug Effect indicated that increases were observed when 100 mg of progesterone was combined with the moderate dose of triazolam (Figure 2.2, panel B) and increases also occurred when 200 mg of progesterone was combined with the high dose of triazolam (panel C) (p <.05). Simple effect analyses of ratings of VAS Bad Drug Effect indicated that increases occurred when either dose of progesterone was combined with the moderate dose of triazolam (panel E) and when 200 mg of progesterone was combined with high dose of triazolam (panel F) (p < .05). Simple effects analyses of ratings of VAS Pay for Drug revealed an interaction primarily related to a small effect of progesterone at placebo triazolam (panel G); however increased effects were also observed when 200 mg of progesterone was combined with the high dose of triazolam (Graph F) (p < .05). Similar to the trends observed on measures of sedation (Figure 2.1), the combination of progesterone and triazolam delayed the peak effects, compared to the effects of progesterone alone.

Separate and combined effects of progesterone and triazolam were also observed on measures of psychomotor task performance as well as self-evaluations of performance acuity (Table 2.1). Figure 2.3 presents DSST measures of Total Trials Completed (top row), and VAS ratings of Performance Impaired (middle row) and Performance Improved (bottom row). Main effects of triazolam or a triazolam by time interaction were observed on each measure (p < .05). Simple effects analyses indicated that triazolam effects on both DSST Total Trials (Figure 2.3, open squares, panels A through C) and VAS Performance Impaired (open squares, panels D through F) occurred at highest dose of triazolam (0.25 mg/70 kg) 90 through 120 minutes after triazolam administration (p < .05). No triazolam by time interaction was detected on VAS Performance Improved, but the time course was similar to other measures of performance, with peak effects occurring 90 and 120 minutes post-dose.

A main effect of progesterone was observed on VAS Performance Impaired (Table 2.1), with progesterone increasing ratings early in the session (Figure 2.3, panel

D). A main effect of progesterone was also detected on DSST Total Trials (Table 2.1); however minimal effects of progesterone were observed in combination with placebo triazolam (panel A).

A significant interaction between progesterone and triazolam was also detected on each of the measures in Figure 2.3. Simple effects analyses of DSST Total Trials indicated that 200 mg progesterone combined with 0.12 mg/70 kg triazolam significantly decreased trial completion (Figure 2.3, panel B) and on associated measures, such as number of correct trials on the DSST ($p < .05$). Simple effect analyses indicated increases in VAS Performance Impaired ratings at both active dose of progesterone combined with 0.12 mg/70 kg triazolam (panel E) and by 200 mg combined with 0.25 mg/70 kg (panel F) ($p < .05$). Simple effects analyses of VAS Performance Improved indicated ratings were increased by the combination of 100 mg of progesterone and the moderate dose of triazolam (panel H) and by 200 mg combined with the high dose of triazolam, although the magnitude of the effect was small (panel I). Similar to other measures (Figure 2.1 and 2.2), progesterone administration delayed the time to the peak effects as triazolam dose increased.

Significant main effects of both progesterone and triazolam, as well as a significant interaction between progesterone and triazolam, were observed on number of responses per un-popped balloon on the BART (Table 2.1). Follow-up testing of the progesterone by triazolam interaction indicated an effect of progesterone at each dose of triazolam and an effect of triazolam only at 100 mg dose of progesterone ($p < .05$). Examination of these data indicated significant variability in the number of responses per balloon occurring during baseline sessions, with small magnitude increases across time following placebo progesterone administration and a small magnitude decrease following either 100 or 200 mg progesterone. This effect was particularly evident at the 0.12 mg/70 kg dose of triazolam. No differences in number of responses per balloon were observed at any assessment, indicating that progesterone and triazolam effects on this task are related to variability in performance as opposed to any reliable neuropharmacological effects of either compound.

Separate and combined effects of progesterone and triazolam were also observed on cardiovascular measures (Table 2.1). Follow up analyses indicated small magnitude increases in each cardiovascular measure across time, but no systematic

changes due to administration of either drug were observed at any assessment. These trends indicate that statistical significance was related to variability at baseline measurements as well as across assessments and not systematically related to pharmacological modulation of cardiovascular measures.

Additional data (means and standard errors for each measure collected) are available in Appendix B.

DISCUSSION

The present study used subjective, performance and cardiovascular measures to evaluate the effects of exogenous progesterone, alone and in combination with triazolam, in healthy, pre-menopausal women. The results of this study demonstrated that both progesterone and triazolam, alone, produced sedative-like effects, and that their effects in combination were greater than those of either compound in isolation. In addition, the drug combination also shifted the time course of triazolam effects, with peak effects occurring later in the session.

Triazolam, when administered alone, engendered prototypical subjective, performance and cardiovascular effects, most consistently at the highest dose (0.25 mg/70 kg). Peak behavioral effects of 0.25 mg/70 kg triazolam occurred between 1.5 and 2.5 hours after dose administration, which is consistent with previous reports (Rush et al., 2003; Simpson & Rush, 2002). Progesterone alone also produced sedative-like effects on a variety of subjective effect measures at both doses, with peak behavioral effects occurring between 1.25 and 1.75 hours after progesterone administration (30 and 60 minutes post triazolam administration). The magnitude and time course of these effects were somewhat different than have previously been reported. Sedative-like effects of progesterone are typically limited to administration of higher oral doses than were used in this study, or to routes of administration with greater bioavailablity (i.e., intramuscular administration) (Freeman et al., 1993; Soderpalm et al., 2004; de Wit et al., 2001). In addition, peak effects of oral progesterone have previously been reported to occur between 2 and 2.5 hours after drug administration (Sofuoglu, et al., 2001, 2002; Chakmakjian & Zachariah, 1987). The most likely factor contributing to the more rapid onset and increased magnitude of sedative-like effects in the present study was the administration of a moderate-fat snack thirty minutes after progesterone administration, as the administration of a moderate-fat meal has been reported to increase

progesterone bioavailability (Simon et al., 1993; Stanczyk, 1999). However, other factors, such as participant characteristics (i.e., participants in this study were light drinkers, had limited or no previous benzodiazepine exposure, and were taking oral birth control), could also have contributed to the pharmacodynamic effects observed in the present study.

The combined effect of progesterone and triazolam resulted in enhanced subjective, performance and cardiovascular effects, as compared to those of triazolam or progesterone in isolation. The combination of progesterone and triazolam also shifted the time course of peak progesterone effects. When administered alone, progesterone effects were limited to initial assessments (1.25 to 1.75 hours after progesterone administration). However, when progesterone was combined with either active dose of triazolam, the peak effects were shifted to time points in the latter portion of the session (135 through 195 minutes after progesterone administration, or 90 through 150 minutes after triazolam administration). Generally, both doses of progesterone combined with the moderate dose of triazolam (0.12 mg/70 kg) produced an enhanced effect, while only the 200 mg dose of progesterone produced increased effects at the high dose of triazolam (0.25 mg/70 kg). In addition, peak effects of progesterone in combination with the 0.12 and 0.25 mg/70 kg dose of triazolam occurred at times in which progesterone, alone, had minimal subjective, performance or cardiovascular effects.

The enhanced magnitude of triazolam effects occurring at times in which progesterone, alone, had minimal effects and the shifted time course of progesterone effects may be associated with circulating levels of the neuroactive progesterone metabolites allopregnanolone and TH-DOC which are $GABA_A$ ligands and can produce behavioral effects similar to alcohol and benzodiazepines (Lambert et al., 1995, 2009; Grant et al., 2008). Although TH-DOC and pregnanolone levels rise after progesterone administration, the clinical time course of these hormone derivatives have not been established. After oral progesterone administration, peak progesterone and allopregnanolone levels occur at 2 hours, with levels remaining elevated above baseline for a total of 5 and 8 hours, respectively (Andréen et al., 2006; Nahoul et al., 1993). In the absence of blood levels of progesterone and its metabolites, the relative impact of each neurosteroid is not clear. However, the time course of these hormones may help inform the basis of the enhanced effect of the combination of progesterone and triazolam during times when progesterone alone engendered minimal subjective or performance

effects (i.e., 135 through 195 minutes after progesterone administration).

Although progesterone activity at $GABA_A$ receptor complex is the most well-characterized effect, other neurotransmitter systems may be involved when progesterone is combined with triazolam. Progesterone and its metabolites may engender some effects via modulation of other neurotransmitter systems, as these neurosteroids have been shown to rapidly modulate dopamine, serotonin, opiate, glutamate and nicotinic acetylcholine systems (Pluchino et al., 2006; Lena et al., 1993). Further research is necessary to determine the specificity of neurosteroid modulation of benzodiazepines.

Overall, the combined effect of progesterone and triazolam yielded rather consistent effects on a variety of sedative-like measures. However, seemingly incongruent effects on subjective measures of drug effect and performance ability emerged in this study. VAS ratings of Good Drug Effect and Bad Drug Effect and similarly, ratings of Performance Impaired and Performance Improved were simultaneously increased after administration of the combination of progesterone and both active doses of triazolam. Many drugs of abuse engender simultaneous positive and negative drug effects, and it has been proposed that the balance between these opposing effects may determine how readily a drug is self-administered (Foltin and Fischman, 1991). Subjective effect ratings of performance ability and psychomotor task performance were also somewhat disparate. When progesterone was administered in isolation, ratings of VAS Performance Impaired increased while DSST Total Trials, an objective measure of performance, was not substantially affected. Triazolam impaired DSST task performance, while simultaneously increasing ratings of both performance impairment and improvement. Inconsistencies between self-ratings of performance and objective measures of behavior have been previously reported (Marczinski et al, 2008; Brumback et al., 2007; Marczinski & Fillmore, 2006; Roache & Griffiths, 1985), although it is not clear whether changes in dimensions of performance that were not measured in the present study (e.g., reaction time, response inhibition, coordination) could have influenced participant's ratings of improved performance.

BART performance was not sensitive to the effects of triazolam or progesterone, which is consistent with previous reports that have examined the acute effects of dose ranges of other GABAergic drugs, such as diazepam (Reynolds et al., 2004) and alcohol

(Reynolds et al., 2006), suggesting that performance on this measure of impulsivity is generally insensitive to the acute effects of GABAergic drugs in healthy participants. Similarly, cardiovascular activity was minimally affected by the dose range of progesterone and triazolam tested in the present study, which is also consistent with previous studies reporting minimal effects of either progesterone or triazolam (at similar doses) on cardiovascular activity (Sofuoglu et al., 2002, 2004; Haga et al., 2003; Simpson & Rush, 2002). The present study extends these previous results by demonstrating that the combined effects of triazolam or progesterone also have negligible effects on BART performance and cardiovascular activity.

Some limitations to the present study should be noted. In the current study, both active doses of progesterone engendered some sedative-like effects in isolation, and generally only the highest dose of triazolam produced statistically significant effects compared to placebo. Future studies should examine progesterone and benzodiazepine interactions with a wider range of benzodiazepine doses and include progesterone doses that engender minimal measurable effects when administered in alone. Another limitation to this study was the unexpected discordance of the onset of peak effects of progesterone and triazolam, with peak progesterone effects occurring approximately 1 hour prior to the peak effects of triazolam. Although the study was designed to examine concomitant peak effects, the separate peak of effects of each compound allowed for interesting interactions to emerge. Experimental sessions were conducted only during the 7-day placebo phase of participants' oral contraceptive regimen. Because the study consisted of 9 sessions, it could not be completed during one week, which resulted in some sessions being separated by several weeks. However, this design allowed for sessions to occur when progesterone and estradiol were at nadir levels, permitting controlled manipulation of progesterone levels. A similar design was used to assess hormonal modulation of the discriminative stimulus effects of the stimulant drug *d*-amphetamine in women (Lile et al., 2007). Separating sessions could also have reduced the likelihood that tolerance or sensitization would occur.

These results, along with a growing body of literature, support the hypothesis that progesterone modulates the behavioral effects of GABAergic drugs (e.g., Grant et al., 1997; Green et al., 1999; Kroboth et al., 1985; McAuley et al., 1995). In addition, these data suggest that progesterone may be one factor among many that contributes to the gender differences observed in benzodiazepine misuse, whereby women are at an

elevated risk of developing dependence on benzodiazepine medications compared to men. Taken together, these studies should inform potential strategies in gender-specific prevention and treatment of sedative drug use.

Although an interaction between progesterone and triazolam was observed in this study, this interaction occurred after the effects of progesterone had dissipated. It is unclear if the magnitude of this interaction would be enhanced if simultaneous peak effects were generated, or if the interaction was due to progesterone metabolites, which emerge after the peak effects of progesterone. To more thoroughly investigate the mechanisms of this interaction, the final study will adjust the timing of progesterone and triazolam administration so that simultaneous peak effects emerge. In addition, this study will also complement the results of Studies 1 and 2 as it incorporates drug discrimination methodology to more thoroughly assess the neuropharmacological effects of progesterone, alone and combination with triazolam.

Table 2.1. F-values of selected measures for which a significant main effect or interaction was obtained.

	Triaz	Tz x Time	Prog	P x Time	Triaz x Prog	Tz x P x Time
Self-Report Measures						
VAS						
Stimulated	3.28		7.11		2.77	
Stressed	13.76				7.71	
Sedated		2.30	12.01			
Anxious			4.16		3.20	
Light-Headed	11.42		7.01		3.33	
Sleepy	9.11					
Sick To Stomach	6.61				4.28	
Shaky	12.27		3.71			
Jittery	17.29					
Depressed					2.47	
High	6.38		6.09		3.09	
Euphoric	6.71		4.52			
Active			8.79			
Alert	3.22		8.72			
Energetic	3.24		10.68			
Drug Effect	17.99	2.49	21.51		2.92	
Good Drug Effect	5.55		3.48		3.54	
Bad Drug Effect	3.43		6.95		2.87	
Performance Impaired	15.93	2.00	18.43		3.54	
Performance Improved	5.02				4.98	
Like Drug					4.93	
Pay for Drug	9.06				9.86	
ARCI						
PCAG	11.42	3.11	10.55			
A					3.16	
ARS						
Sedation	7.75		11.77			
POMS						
Anxiety	8.19			4.48		
Vigor			11.23			
Fatigue	6.12		3.04		3.88	
Elation			5.41		2.86	
Arousal			10.37			
Total Positive			7.42		3.11	
Performance Measures						
DSST						
Total Trials	20.84	4.07	8.25		2.60	
Prop Correct	4.25				3.60	
BART						
Popped	3.01					
# Responses	6.07		8.55		4.58	
Cardiovascular Measures						
HR			3.83		2.70	
Systolic	10.78		3.26			1.72
Diastolic			3.15	1.98	3.27	

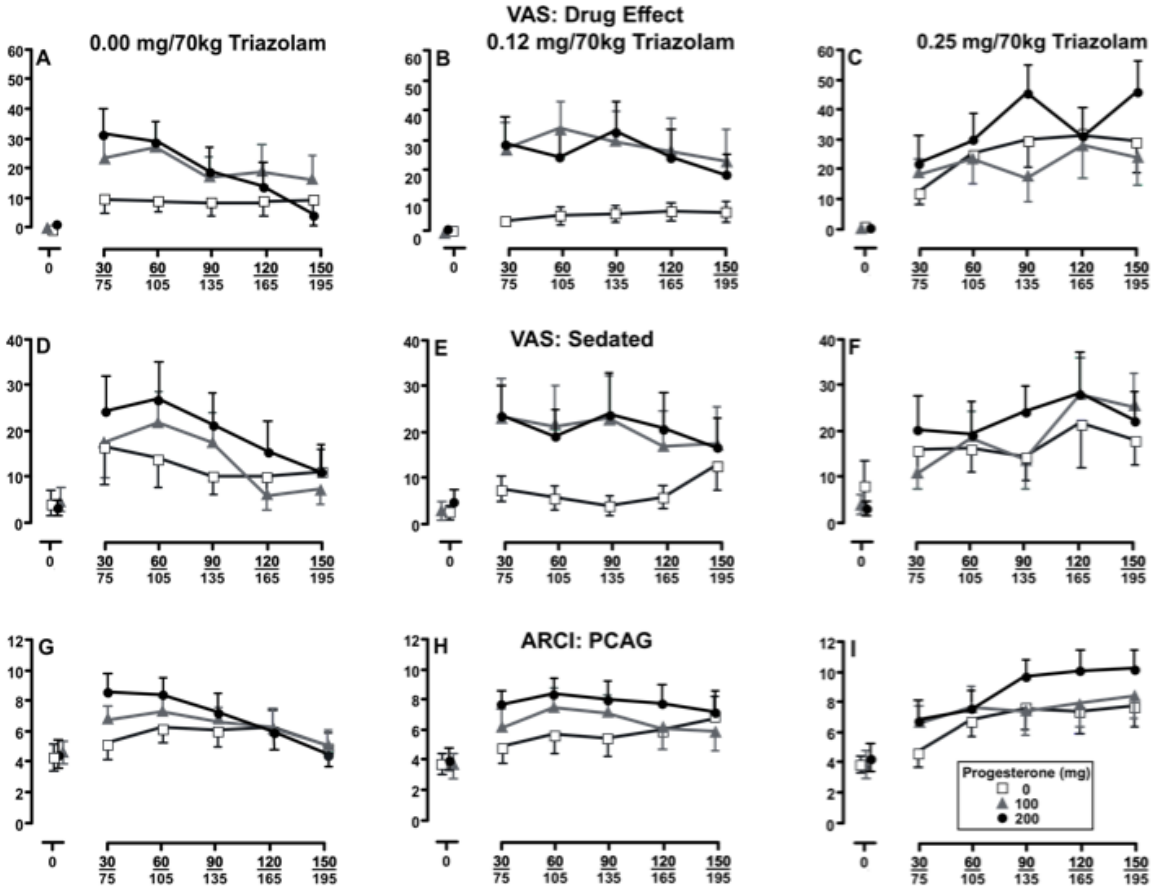

FIGURE 2.1. Mean ratings of VAS Drug Effect (top panel), VAS Sedated (middle panel) and ARCI PCAG Scale (bottom panel) as a function of triazolam dose, progesterone dose and time following triazolam/progesterone administration. Data points represent means (±S.E.M. denoted by the error bars) of 11 participants. Different y-axis scales are used across the three measures.

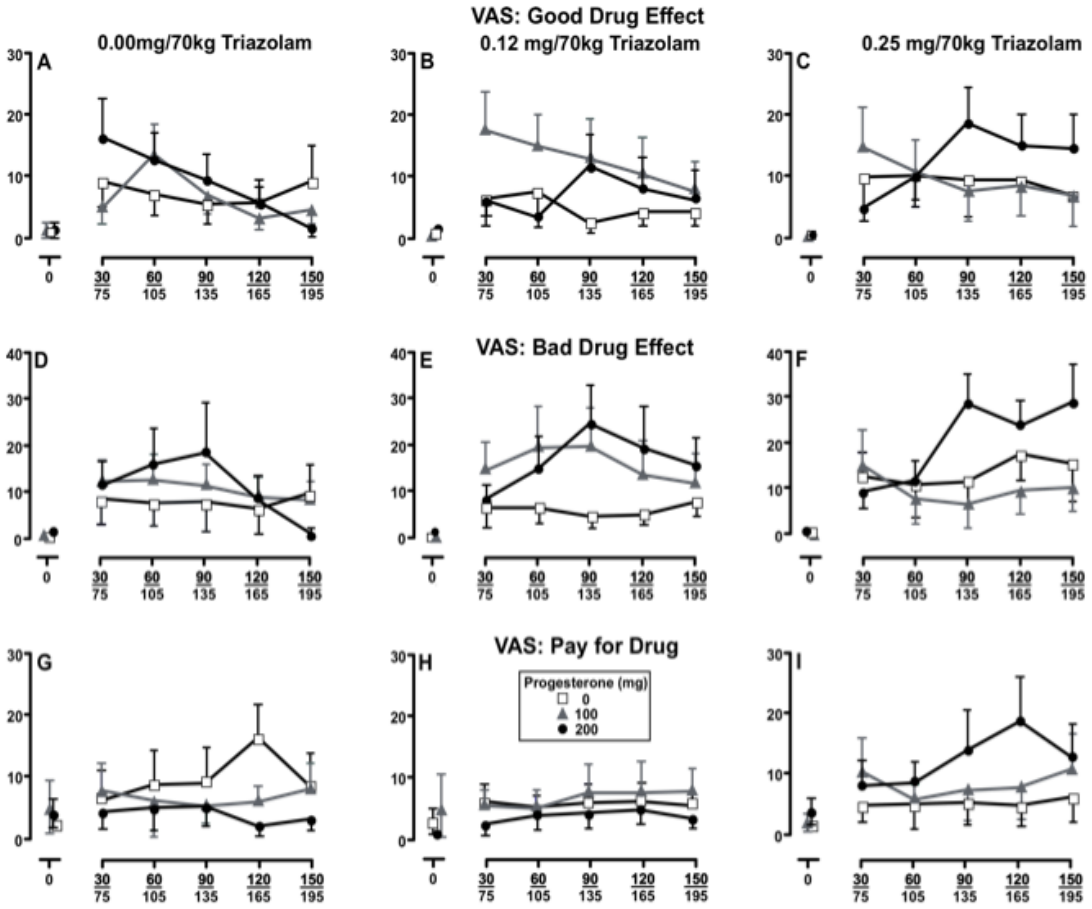

Figure 2.2. Mean ratings of VAS Good Drug Effect (top panel), VAS Bad Drug Effect (middle panel) and VAS Pay for Drug (bottom panel) as a function of triazolam dose, progesterone dose and time following triazolam/progesterone administration. Data points represent means (±S.E.M. denoted by the error bars) of 11 participants. Different y-axis scales are used across the three measures.

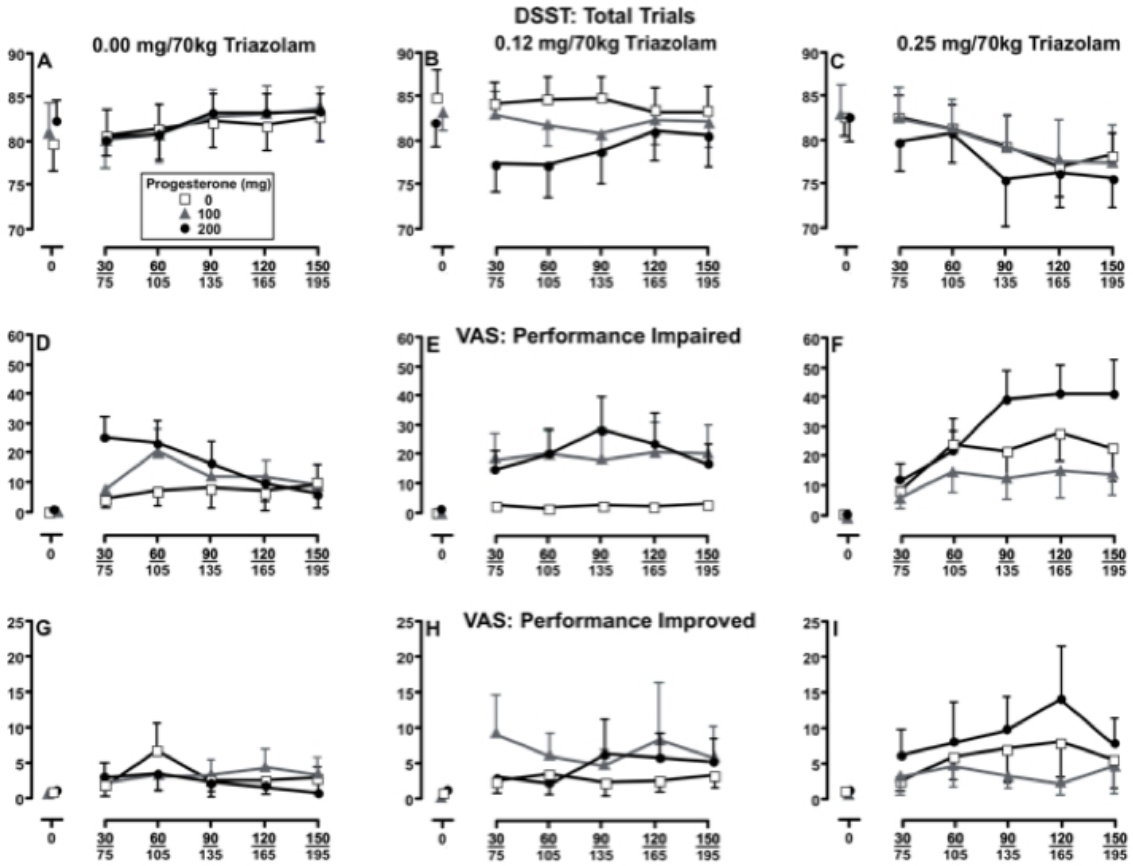

Figure 2.3. Mean trials completed on DSST Total Trials (top panel), ratings of VAS Performance Impaired (middle panel) and VAS Performance Improved (bottom panel) as a function of triazolam dose, progesterone dose and time following triazolam/progesterone administration. Data points represent means (±S.E.M. denoted by the error bars) of 11 participants. Different y-axis scales are used across the three measures.

CHAPTER 4

STUDY 3: Progesterone modulation of the discriminative stimulus, subjective and performance effects of triazolam in healthy, pre-menopausal women

INTRODUCTION

Neurosteroids (e.g., progesterone, allopregnanolone) are abundantly present in premenopausal women, with plasma concentrations varying as a function of menstrual cycle phase. Both pre-clinical and clinical research indicates that neurosteroids modulate receptor systems and alter drug effects (McAuley et al., 1995; White et al., 2002; Justice et al., 1999; Lynch et al., 2002; Lile et al., 2007). Progesterone and its metabolites, allopregnanolone, TH-DOC, and pregnanolone, have non-genomic effects at binding sites on neuronal membrane-bound receptors and also modulate several neurotransmitter systems including GABA, dopamine, opiate, glutamate and nicotinic acetylcholine systems (Pluchino et al., 2006; Lena et al., 1993). In particular, both in vitro and in vivo studies have shown evidence that progesterone and its metabolites modulate activity at the $GABA_A$ receptor complex, with these neurosteroids acting as ligands at extracellular, steroid-specific recognition sites on $GABA_A$ receptors, having affinities that are comparable to those of many benzodiazepines (Paul & Purdy, 1992). The neuroactive metabolites also dose-dependently increase the effects of benzodiazepines on GABA-induced Cl^- currents, indicating that there is a non-genomic, receptor-level interaction between benzodiazepines and neurosteroids in vitro (Paul & Purdy, 1992; Bertz et al., 1995).

Pre-clinical research has indicated that menstrual cycle phase modulates the some of the effects of GABAergic drugs. The discriminative stimulus effects of ethanol are enhanced during the mid-luteal phase, when endogenous progesterone levels are elevated (Grant et al., 1997, Green et al., 1999). Study 1 demonstrated cycle modulation of benzodiazepine effects in pre-menopausal women, with potentiation of the discriminative stimulus effects of triazolam occurring during the mid-luteal phase (relative to the early follicular phase). However, there is little or no evidence for cycle modulation of the subjective and performance effects of GABAergic drug effects (i.e., triazolam, ethanol) in pre-menopausal women (Holdstock & de Wit, 2000; Rukstalis & de Wit, 1999). One potential reason for the inconsistent clinical results could be due to the sensitivity of drug discrimination methodology, as cycle modulation of the discriminative

stimulus effects of drugs may be more sensitive to neuropharmacological manipulations than subjective or performance measures (Kelly et al., 2003).

Examining drug effects across the cycle provides information about how the endogenous hormonal milieu modulates drug effects, but does not provide a direct measure of the relative effect of a particular hormone, due to several hormones simultaneously fluctuating throughout the cycle. For example, during the mid-luteal phase, progesterone levels increase, but estradiol levels are elevated as well, making it difficult to discern the effect of progesterone alone. To determine the independent effect of progesterone and its primary metabolites, the effects of GABAergic drugs have also been examined after exogenous progesterone administration. Administration of oral micronized progesterone enhanced the sedative, memory and performance effects of intravenous triazolam in post-menopausal women (McAuley et al., 1995). In addition, the results of Study 2 indicated that oral micronized progesterone enhanced the subjective and performance effects of oral triazolam in healthy, premenopausal women during the early follicular phase, when endogenous progesterone and estrogen are at nadir levels. These studies provide evidence that acute administration of progesterone enhances some behavioral effects of benzodiazepines. However, in both of these studies, the onset and peak effects of progesterone occurred prior to the peak effects of triazolam and interactions between progesterone and triazolam were detected after peak progesterone effects had occurred. The asynchronous time courses for progesterone and triazolam suggest that their interactions might have be underestimated, or driven predominantly by neuroactive progesterone metabolites, specifically allopregnanolone, which remains elevated several hours after oral progesterone levels peak.

The purpose of the present study was to determine the independent and combined discriminative stimulus, subjective and psychomotor effects of progesterone and triazolam in healthy adult pre-menopausal women using a dosing schedule that should allow for peak drug and hormone effects to occur concurrently. This arrangement allows for a close examination of the potential interaction between the two compounds and provides information regarding the hormonal constituents that may drive the interaction (i.e., the parent hormone progesterone vs. the progesterone metabolites that occur several hours after progesterone levels peak). Drug discrimination methodology was chosen to more precisely examine the neuropharmacological effects of progesterone, alone and combination with triazolam, as drug discrimination has been shown to be an effective tool in examining pharmacological changes mediated by

receptor-based interactions (Colpaert, 1999; Kelly et al., 2003).

METHOD

Participants

Recruiting procedures, medical screening protocols and inclusion/exclusion criteria were identical to those used in Study 2.

Fourteen participants were enrolled in the study. Three participants withdrew from the study for reasons unrelated to the study protocol, two were discontinued from the study because they did not acquire the drug discrimination; data from these five participants were not included in the data analyses. Nine participants (8 Caucasian, 1 African American) completed the study. The participants ranged in age from 18 to 30 years (median = 22 years) and in weight from 55 to 93 kilograms (median = 65.95 kg; BMI range = 21 to 31, median = 22.1). All participants were non-smokers. Alcohol use ranged from less than 1 to 8 alcohol drinks per week (median = 4) and caffeine use ranged from 0 to 200 mg of caffeine per day (median = 80 mg). Participants reported no psychoactive drug use in the month prior to study participation and no drug use was detected during the study with daily urinalysis testing. Urine screens for pregnancy were also negative throughout participation. Participants were compensated for their participation.

Design

A double-blind, placebo-controlled, randomized design was used to assess the effects of three within-subject variables: progesterone dose (0 and 100mg), triazolam dose (training doses: 0.00 and 0.25 mg/70 kg, test doses: 0.06 and 0.12 mg/70 kg), and time (assessments occurring prior to and 30, 60, 90, 120 and 150 minutes after dose administration) on the discriminative stimulus and other behavioral effects of triazolam during the early follicular phase of the menstrual cycle (i.e., placebo phase of the oral birth control regimen), when estrogen and progesterone levels are at their nadir.

The results of Study 2 indicated that oral progesterone, when administered with a moderate-fat snack, produced peak behavioral effects 75 to 105 minutes post-dose, while oral triazolam effects occur 90 to 150 minutes post dose. In an effort to examine the concurrent peak effects of these medications, progesterone and triazolam were administered simultaneously.

Drugs

Doses of progesterone and triazolam were prepared by the University of Kentucky Investigational Pharmacy. Progesterone (0 and 100 mg; Prometrium®) and triazolam (0.00, 0.06, 0.12 and 0.25 mg/70 kg) were prepared in size 00 and 0 distinct opaque capsules, respectively, each with cornstarch filler. Placebo capsules contained only cornstarch filler. Both progesterone and triazolam doses were delivered orally.

Schedule

Participants completed one training session prior to the experimental sessions to acquaint them to the study procedures and to establish consistent and accurate performance on computerized behavioral tasks. This practice session was conducted irrespective of menstrual cycle phase but within one week of the initiation of the experimental sessions.

After a baseline assessment, progesterone and triazolam were administered simultaneously. Fifteen minutes after drug administration, participants consumed a moderate-fat snack to enhance progesterone absorption (Simon et al., 1993; Stanczyk, 1999). Assessments were repeated at 30-minute intervals for 3 hours after drug administration, and consisted of the Drug Discrimination Task (post-dose assessments only), Visual Analog (VAS) and Adjective Rating Scales (ARS), Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS), Digit Symbol Substitution Task (DSST), Balloon Analog Risk Task (BART) and heart rate and blood pressure measurement (Sentry II, NBS Medical, Costa Mesa, CA). Only the drug discrimination procedure will be described here, as it is somewhat different than the procedure used in Study 1. The VAS, ARS, ARCI, POMS, DSST and BART are exactly the same as those described in Study 2.

Assessment Tasks

Drug discrimination task

During this task, two circles labeled with a letter code (e.g., “Drug A” and “Not Drug A”) were displayed on the computer screen, each associated with a training dose condition. Counters were displayed directly beneath the circles. A mouse controlled the location of a cursor on the screen, and mouse button clicks with a cursor positioned on a circle increased the counter associated with that circle according to a Fixed Interval (FI) 1-s schedule. The cursor could alternate across the circles without any consequence under the FI schedule (i.e., no changeover delay). Up to 60 points could be allocated across the two options. The dependent variable for this task was the percent of responding on the active drug-appropriate option.

The drug discrimination task in this study was slightly different than that used in Study 1. This study established the discrimination using two options labeled ‘Drug’ and ‘Not Drug,’ rather than ‘Drug A’ and ‘Drug B.’ The Drug v. Not Drug procedure has been reported to establish discrimination behavior that is more consistent with the pharmacological activity and subjective effects of medications than other procedures (e.g., the Drug A v. Drug B task used in study 1) (Preston & Bigelow, 2000; 1994; Preston et al., 1992).

Sampling, control and testing phases were presented during the study. Sampling and control phases were conducted without regard to menstrual cycle phase. The test phase was scheduled to coincide with the early follicular phase of the menstrual cycle (i.e., placebo phase of the oral birth control regimen), when endogenous levels of both progesterone and estrogen are at nadir levels. Participants completed the Test Phase across 2 to 4 consecutive menstrual cycle phases.

Sampling Phase

The sampling phase consisted of two experimental sessions. On each of the two sessions, participants were informed that the medication she was receiving was ‘Drug A’ (0.25 mg/70 kg triazolam and 0 mg progesterone). A unique letter code (i.e., ‘Drug A’) was used for each participant. The following written instructions were available to participants throughout this phase:

"This is Drug A. During the next two days, you will receive Drug A. Pay close attention to how Drug A makes you feel. In the future, you will not be told which dose you have received and you will have to decide whether or not you received Drug A. During the next two days your earnings from the Drug Identification Task will be based on how many points you allocate to the Drug A option. Please do your best to allocate all the points to the Drug A option."

Control Phase

The control phase was used to determine whether participants had acquired the drug discrimination. Daily schedules during the control phase were identical to those during the sampling phase, with the exception that the participants were blind to the identity of the administered drug (i.e., Drug A, or Not Drug A) until the end of the session. The training dose of triazolam (0.25 mg/70 kg, Drug A) or placebo (Not Drug A), and placebo progesterone, were administered randomly under double-blind conditions, with each triazolam dose presented at least twice, but the same dose was never administered on more than three consecutive days. The criterion for acquisition of drug discrimination was ≥ 80% of responses allocated to the drug-appropriate option during the last assessment of the session (150 minutes post-dose) for five consecutive sessions. If the acquisition criterion was not met in 12 sessions, participants were dismissed from the study. Participants who met criteria did so within 5 to 12 sessions. Performance payment was contingent on discrimination responding, with 10 cents earned for each correct response (i.e., points) allocated to the option associated with the dose administered that day. The following written instructions were available to participants:

“Today we will not tell you whether you received Drug A or Not Drug A. Instead, you will have to decide whether you received Drug A or Not Drug A. If you think you received Drug A, and in fact you did receive Drug A, you can earn extra money by responding on the button labeled Drug A. If you do not think you received Drug A, and in fact you did not receive Drug A, you can earn extra money by responding on the button labeled Not Drug A. For example, if you feel that you did not receive any drug today, you should respond on the button labeled Not Drug A. Similarly, if you think that you received a drug, but it feels different than Drug A, you should respond on the button labeled Not Drug A. You can change your drug identifications throughout today's session based on

what you think at the time.

At the end of some sessions, the computer will present a screen that will tell you if you received Drug A or Not Drug A. The number of points that you accumulated on the correct button will then be converted to money and you will be told how much bonus money you earned during today's session. At the end of some sessions, we may not be able to tell you whether you received Drug A or Not Drug A. On the days that we cannot tell whether you, your bonus earnings will be the average of the amount you earn on days in which we can tell you that you received Drug A or Not Drug A."

Test Phase

During the Test Phase, dose-response generalization functions were established for triazolam (0.00, 0.06, 0.12, and 0.25 mg/70 kg) alone and in combination with progesterone (0.00 and 100 mg). One permutation of progesterone (0 and 100 mg) and triazolam (0.00, 0.06, 0.12, and 0.25 mg/70 kg) was administered during each experimental session in random order, for a total of 8 sessions. On days that participants received a training dose (i.e., 0.00 or 0.25 mg/70 kg oral triazolam with 0 mg sublingual progesterone), participants received feedback regarding the accuracy of their performance at the end of the session and payment was contingent upon accuracy (as in the Control Phase). The instructions presented during the Control Phase were also available during Test Phase sessions.

Data Analysis

Drug effects were analyzed using repeated-measures ANOVA with triazolam dose, progesterone dose and time as factors. Interactions were evaluated using simple-effects analyses.

RESULTS

Drug Discrimination

Figure 3.1 presents mean drug-appropriate responding as a function of triazolam and progesterone dose during control and test sessions. During control sessions, participants met the drug discrimination acquisition criterion in a mean of 7 sessions (range of 5 to 12, median = 8). Across the final 5 control sessions, all participants emitted approximately 0 % and 99% drug appropriate responding 150 minutes after

placebo and active drug administration, respectively. During the test phase, training dose conditions (0.00 and 0.25 mg/70 kg) engendered 11% and 100% triazolam-like responding. The test doses (0.06 and 0.12 mg/70 kg) produced intermediate triazolam-like responding, approximately 30% and 50%, respectively. This intermediate responding was due to averaging data from participants identifying the dose as either drug-like or non-drug-like (i.e., quantal responding by individual subjects). Progesterone alone engendered 27% drug-like responding, resulting from two participants identifying 100 mg progesterone as drug-like. Progesterone in combination with triazolam did not modify drug discrimination responding at any triazolam dose.

Subjective Effects

Triazolam alone produced prototypical sedative-like effects on multiple self-report measures, including increases in ARS Sedation, VAS Sedated, Sleepy and Performance Impaired, POMS Fatigue and ARCI PCAG Scale (Table 3.1). In addition, a main effect of triazolam or an interaction of triazolam and time was also observed for VAS Light-Headed, High, Energetic and Drug Effect and POMS Vigor, and Arousal (Table 3.1). Figure 3.2 presents VAS ratings of Sedated (top row), Performance Impaired (middle row) and Drug Effect (bottom row) as exemplars. As illustrated in Figure 3.2, peak effects of triazolam occurred 60 through 90 minutes after administration on each measure.

Independent of triazolam, progesterone also engendered sedative-like effects, including VAS Sedated, Sleepy and Performance Impaired (Table 3.1). In addition, a main effect of progesterone or an interaction of progesterone and time was also observed for VAS ratings of Drug Effect and Good Drug Effect (Table 3.1). Peak effects of progesterone also occurred 60 to 90 minutes after administration on each measure.

The combination of progesterone and triazolam engendered small magnitude increases in subjective effects, compared to either dose alone (Figure 3.2). The effects of progesterone on the response to triazolam appeared to be additive; that is, the magnitude of the increase in subject ratings associated with dose combinations was not greater than that of progesterone alone. In addition, progesterone delayed the time at which peak effects occurred for the high dose of triazolam (0.25 mg/70 kg; 90 through 150 minutes).

Performance Effects

Triazolam produced prototypical sedative-like effects on measures of psychomotor task performance, with a main effect of triazolam detected on DSST trial rate and accuracy (Table 3.1). Independent of triazolam, progesterone decreased trial accuracy (Table 3.1). Similar to what was observed for the combined effects of progesterone and triazolam on subjective effects, small magnitude additive effects were apparent for trial accuracy.

No independent or combined effects of progesterone or triazolam were observed on BART performance.

Cardiovascular Effects

Significant triazolam and progesterone effects were observed on diastolic blood pressure (Table 3.1); however, these effects were small in magnitude (approximately 5 mm Hg) and limited to specific points in time. It is unlikely that these changes represented systematic drug effects or drug interactions.

Additional data (means and standard errors for each measure collected) are available in Appendix C.

DISCUSSION

The present study used drug discrimination and subjective, performance and cardiovascular measures to examine the effects of progesterone, alone and in combination with triazolam in healthy, pre-menopausal women. Consistent with previous studies, triazolam alone engendered a broad range of sedative-like effects in a dose-related manner, with peak effects occurring 60 to 90 minutes post dose (Greenblatt et al., 2005; Rush et al., 2003; Simpson & Rush, 2002; Rush & Ali, 1999). Progesterone alone produced small magnitude increases in sedative-like measures with a similar time course. The combination of progesterone and triazolam engendered additive effects on subjective and performance effects and delayed the time at which the peak effects of the 0.25 mg/70 kg dose of triazolam occurred. Triazolam functioned as a discriminative stimulus, but progesterone did not consistently substitute for or modulate the discriminative stimulus effects of triazolam

One aim of this study was to examine the effects of progesterone and triazolam

under conditions in which the peak effects for the hormone and drug occurred at similar times. To accomplish this goal, progesterone and triazolam were administered simultaneously, as Study 2 has indicated that peak effects emerge at similar times. This approach was successful with peak effects of both progesterone and triazolam occurring 60 to 90 minutes post-dose. Worth mentioning is that self-reported and performance effects of progesterone alone are not typically observed unless significantly higher oral doses (600 to 1200 mg) or routes of administration with greater bioavailablity (i.e., intramuscular administration) are administered (Freeman et al., 1993; Soderpalm et al., 2004; de Wit et al., 2001; van der Meer et al., 1982). These results replicate the results of Study 2 in which doses of progesterone (100 and 200 mg PO) also increased ratings of several sedative-like measures and engendered decreases in psychomotor task performance. The effects of progesterone may have been enhanced in that study, and the present study, due to the administration of moderate-fat snack 15 minutes after progesterone administration, which has been reported to increase progesterone bioavailability (Simon et al., 1993; Stanczyk, 1999).

A second aim of the study was to examine the neuropharmacological effects of progesterone, alone and in combination with triazolam, using a drug discrimination methodology. Progesterone alone did not substitute for the training dose of triazolam, and concurrent progesterone administration did not alter the discriminative stimulus effects of triazolam. These data do not suggest a common receptor mechanism of action for progesterone and triazolam. It is possible that the sedative effects of progesterone were not mediated by a GABAergic mechanism, although in vitro and pre-clinical in vivo research has clearly documented GABAergic interactions between neurosteroids and GABAergic agents, progesterone and its metabolites have also been shown to modulate multiple receptor systems, including dopamine, serotonin, opiate, glutamate and nicotinic acetylcholine receptor systems (Pluchino et al., 2006; Lena et al., 1993). However, other interpretations are also plausible. First, only a single, relatively small dose of progesterone was tested. Progesterone may have engendered small, GABA-mediated increases in the effects of the low doses of triazolam that were below the threshold necessary to produce reliable drug-like responding on the drug discrimination task. Second, it is possible that progesterone modulation of triazolam effects is dependent on triazolam dose (Green et al., 1999). There is some evidence to support this possibility in that progesterone effects on the highest triazolam dose (i.e., a shift in the time course of the peak effects of the 0.25 mg/70 kg training dose) were distinct from those occurring at

lower doses. Because this shift was limited to the training dose of triazolam, this enhancement would not have been detected due to the ceiling effect imposed by the drug discrimination procedure. Third, it is possible that progesterone modulation of triazolam effects is dependent on progesterone metabolites, rather than progesterone per se (Lundgren et al., 2003; Majewska et al., 1986). The shift in peak effects of the highest triazolam dose occurred after progesterone effects had dissipated and progesterone metabolites, such as allopregnanolone, would be expected to peak, supporting this possibility. Specifically, allopregnanolone levels increase 2 hours after oral progesterone administration and remain elevated for up to 8 hours (Andréen et al., 2006; Nahoul et al., 1993). The interactions between progesterone and triazolam documented in Study 2 and in previous studies also occurred at times corresponding to the emergence of progesterone metabolites (McAuley et al., 1995).

The drug discrimination results of this study were not consistent with those of Study 1 which demonstrated that the discriminative stimulus effects of triazolam were potentiated during the mid luteal phase, when endogenous progesterone levels were elevated. Several factors could have contributed to these disparate results, including the presence of other neurosteroids, the duration of exposure to neurosteroids and progesterone delivery. The current study used exogenous, oral progesterone, while the previous study relied on naturally occurring changes in endogenous progesterone levels across the menstrual cycle. The progesterone dose used in the current study was selected to engender systemic progesterone levels comparable to those of the mid luteal phase (Simon et al., 1993; Stanczyk, 1999). However, during the mid luteal phase, there is a broader milieu of hormones of present, including estrogen and progesterone metabolites, such as allopregnanolone (Genazzani et al., 1998). The relative influence of estrogen on GABAergic drug effect is not clear. However, allopregnanolone is neuroactive and a ligand at the $GABA_A$ receptor, and several cell culture and preclinical studies have identified allopregnanolone as a key component in the hormone-benzodiazepine interaction at the $GABA_A$ receptor (Lambert et al., 2009; Paul & Purdy, 1992). The duration of exposure to neurosteroids may also have influenced sensitivity to the discriminative stimulus effects of triazolam across studies. During the luteal phase of the menstrual cycle, progesterone and allopregnanolone levels remain elevated for approximately 10 days (Genazzani et al., 1998). This cycle-related chronic exposure to neurosteroids may engender genomic-based increases in sensitivity to benzodiazepines (Smith et al., 1998), which may have influenced the mid luteal phase enhancement of

the discriminative stimulus effects of triazolam. In addition, the chronic exposure of progesterone and its metabolites create steady blood levels of neurosteroids, whereas blood levels after exogenous progesterone administration begin to decline 2 hours after administration (Genazzani et al., 1998; Stanczyk, 1999). This difference in onset and duration of action may also help explain why exogenous progesterone engenders a drug-like effect, while similar levels of endogenous progesterone do not typically engender subjective effects. A third factor that could have resulted in differential effects across studies is progesterone delivery. In the current study, progesterone was administered orally, whereas the previous study relied on endogenous changes in progesterone levels across the menstrual cycle. Several studies have documented inconsistent absorption of progesterone associated with oral dosing, with a 40 fold magnitude of differences in absorption occurring across individuals (McAuley et al., 1996; Simon et al., 1993).

This study examined the effects of progesterone, alone and in combination with triazolam under conditions in which the time course of progesterone and triazolam effects were concordant. Prototypical sedative-like effects of triazolam were observed, and consistent with our previous study, progesterone alone also engendered statistically significant increases in sedative-like effects on self-report and performance measures. Progesterone and triazolam engendered additive effects on self-report and performance measures when combined; however, progesterone did not substitute for the triazolam discriminative stimulus, and concurrent progesterone administration had no effect on the discriminative stimulus effects of triazolam. Future studies examining a wider range of progesterone doses and progesterone metabolites in combination with both higher and lower training doses of triazolam and longer-acting benzodiazepines would be useful to further examine receptor-based interactions of progesterone and benzodiazepines.

Table 3.1. F-values of selected measures for which a significant main effect or interaction was obtained. No Triazolam x Progesterone or Triazolam x Progesterone x Time interactions were detected.

	Triazolam	Triazolam x Time	Progesterone	Progesterone x Time
Self-Report Measures				
VAS				
Stimulated				
Stressed				
Sedated	4.41	2.98	7.75	
Anxious				
Light-Headed		1.82		
Sleepy		2.23	7.28	2.70
Sick To Stomach				
High	4.28	2.94		
Euphoric				
Energetic		2.11		
Drug Effect	8.29	3.96		2.77
Good Drug Effect			6.79	2.72
Bad Drug Effect				
Performance Impaired	5.90	2.01	5.86	
Like Drug				
Pay for Drug				
ARCI				
PCAG	5.46	4.00		
ARS				
Sedation	5.47	3.08		
POMS				
Vigor		2.12		
Fatigue	3.29			
Arousal		2.24		
Total Positive				
Performance Measures				
DSST				
Total Trials	13.48	5.22		
Errors	3.54		7.65	
Proportion Correct	5.37		10.63	
Cardiovascular Measures				
HR				
Systolic				
Diastolic		2.86	7.20	

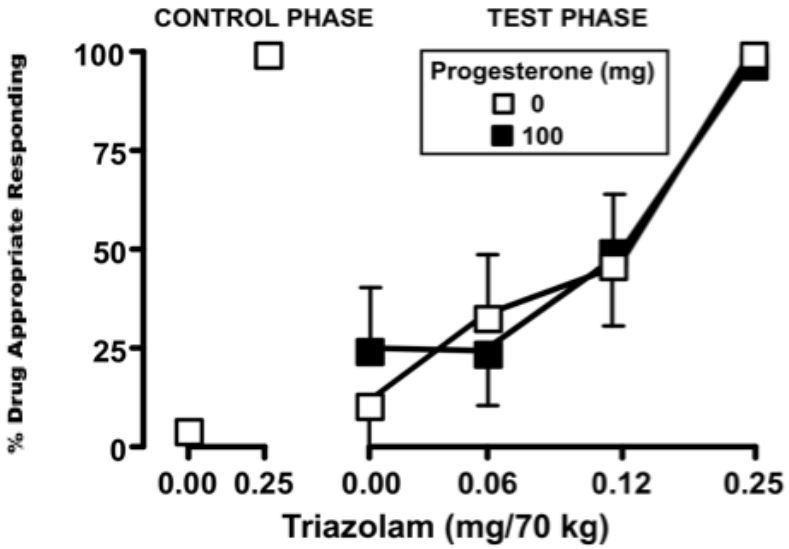

Figure 3.1. Mean triazolam-appropriate responding as a function of triazolam dose and progesterone condition from assessments occurring at 150 minutes post-dose during the control and test phases. Data points represent means of nine participants. Uni-directional error bars represent 1 S.E.M.

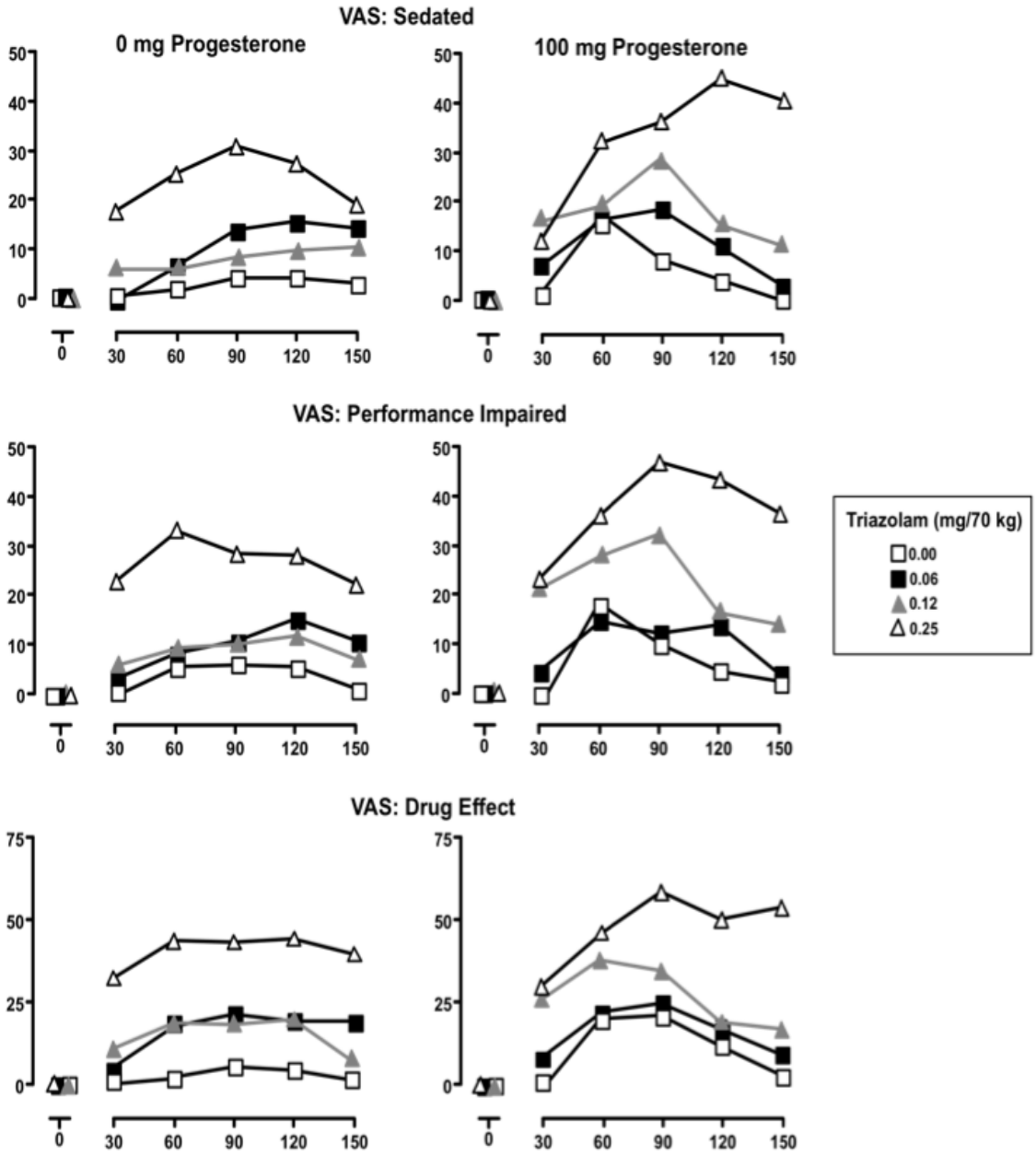

Figure 3.2. Mean ratings of VAS Drug Sedated (top row), VAS Performance Impaired (middle row) and VAS Drug Effect (bottom row) as a function of progesterone dose, triazolam dose and time following drug administration. The left column presents triazolam effects after 0 mg progesterone and the right column presents triazolam effects after 100 mg progesterone. Error bars omitted for clarity.

CHAPTER 5

GENERAL DISCUSSION

The purpose of this series of studies was to determine whether the ovarian hormone progesterone modulates the behavioral effects of the sedative drug triazolam using human laboratory methodologies. The behavioral effects of triazolam and other benzodiazepines are associated with the drugs' positive modulation of the $GABA_A$ receptor complex (Lelas et al., 2002; Licata et al., 2009; Rush et al., 1998). Benzodiazepines function as discriminative stimuli in human models (Rush et al, 2003; Vansickel et al, 2006; Kelly et al., 2003; Oliveto et al., 1992) and the discriminative stimulus effects of benzodiazepines are sensitive to $GABA_A$ modulation (McMahon & France, 2005a; 2005b; Lelas et al., 2000). The sensitivity of this paradigm allows for the examination of the GABA-modulating effects of progesterone, which also exerts potent effects on behavior via modulation of $GABA_A$ receptors (Rupprecht, 2003; Lambert et al., 2009; Bertz et al., 1995; Paul & Purdy, 1992; Majewska, 1992; Majewska et al., 1986).

Overall, the results of these studies indicate that progesterone and its neuroactive metabolites modulate the effects of triazolam. Changes in menstrual cycle associated with increases in progesterone and exogenous progesterone administration modified the effects of triazolam in pre-menopausal women. In addition, exogenous progesterone, independent of triazolam, produced behaviorally active effects at lower doses than have been previously been reported (Freeman et al., 1993; Soderpalm et al., 2004; de Wit et al., 2001; van der Meer et al., 1982). When concordant peak effects of progesterone and triazolam were examined, the combination of progesterone and triazolam engendered additive effects on subjective and performance effects and delayed the time at which the peak effects of the 0.25 mg/70 kg dose of triazolam occurred; however progesterone did not consistently substitute for or modulate the discriminative stimulus effects of triazolam. These effects suggest that the effects of the parent hormone progesterone do not appear to be associated with the same neuropharmacological mechanisms of action as triazolam.

OVERVIEW OF STUDY 1

The first study examined the discriminative stimulus, subjective, performance and cardiovascular effects of triazolam across two phases of the menstrual cycle to

determine if the hormonal milieu unique to each cycle phase would differentially contribute to premenopausal women's sensitivity to triazolam effects. The results of the study clearly indicated that cycle phase modulated triazolam effects, such that during the early follicular phase, the discriminative stimulus effects of all test doses (0.00, 0.06 and 0.12 mg/70 kg) were identified as placebo-like, while only the training dose (0.25 mg/70 kg) was identified as drug-like. In contrast, during the mid luteal phase, only placebo and the low test dose (0.06 mg/70 kg) engendered placebo-like responding, whereas the moderate dose (0.12 mg/70 kg) and the training dose were identified as drug-like. These data suggest that sensitivity to the discriminative stimulus effects of triazolam were modulated by menstrual cycle phase. However, the relative role of progesterone in this interaction is not completely clear. Progesterone and other female sex hormones are at nadir levels during the early follicular phase. During the mid luteal phase, progesterone levels are at their peak, but estrogen levels are also elevated throughout this cycle phase. Therefore, even though there is very strong evidence from in vitro and pre-clinical in vivo research to suggest that progesterone is a neuroactive steroid with activity at the $GABA_A$ receptor, this study did not convincingly demonstrate that the triazolam modulation observed was directly caused by elevations in progesterone.

OVERVIEW OF STUDY 2

Therefore, follow-up studies were conducted to further examine the potential interaction between progesterone and triazolam. The goal of the second study was to isolate and directly manipulate progesterone to determine if the changes in triazolam effects observed previously during the mid-luteal phase were related to progesterone in a dose-dependent manner. The interactions between exogenous progesterone and benzodiazepines had not previously been examined, so it was important to test a range of doses of both progesterone and triazolam to determine whether interactions were dose-dependent. As such, the second study examined the subjective, performance and cardiovascular effects of a range of exogenous progesterone doses, alone and in combination with a dose range of triazolam. The results of this study demonstrated that both progesterone and triazolam, alone, produced sedative-like effects on subjective and performance measures. In addition, the combination of progesterone and triazolam produced effects that were greater than those of either compound in isolation. The results of this study build on those of the previous study, indicating that progesterone alone, had significant effects on behavior at doses thought to engender blood levels

occurring during the mid-luteal phase of the menstrual cycle, and enhanced the behavioral effects of triazolam. The onset of peak effects and duration of effects of progesterone, alone, were most consistent with the time course of the parent compound, progesterone; whereas interactions with triazolam occurred later in time, and were likely associated with increasing levels of progesterone metabolites.

However, even though the results of this study indicated an interaction effect between progesterone and triazolam, due to the timing of dose administration, the peak effects of progesterone and triazolam did not occur simultaneously. The interaction between progesterone and triazolam occurred after the effects of progesterone alone had dissipated. The time course of this interaction indicates that this study may not have captured the potential magnitude of the interaction that may have occurred if the simultaneous peak effects of progesterone and triazolam were examined. Furthermore, it was not clear from these results the degree to which progesterone metabolites were involved in the interaction.

OVERVIEW OF STUDY 3

Therefore, the final study in this series attempted to examine the interaction between progesterone and triazolam under conditions in which the time course of the onset and peak effects of the two compounds were relatively concurrent. In addition, this study implemented drug discrimination methodology to examine whether progesterone and triazolam share discriminative stimulus effects and whether progesterone administration alters the sensitivity of the discriminative stimulus effects of triazolam in order to further elucidate neuropharmacological mechanisms of action.

Consistent with the results of Study 1, triazolam functioned as a discriminative stimulus and engendered prototypical sedative-like effects on subjective and performance measures. Replicating the effects of Study 2, progesterone alone also produced sedative-like effects on subjective and performance measures. However, in contrast to Study 2, this study examined the simultaneous peak effects of progesterone and triazolam. While additive effects of progesterone and triazolam were observed on several measures, no evidence for pharmacological interactions was obtained. In addition, progesterone did not substitute for or modify the discriminative stimulus effects of triazolam, suggesting that progesterone and triazolam do not share a common receptor mechanism.

The additive-like effects of progesterone and triazolam were detected on subjective and performance measures, with the most notable effects occurring at the moderate and high dose of triazolam (0.12 and 0.25 mg/70 kg). Furthermore, progesterone shifted the time course of the effects of this dose to the right. Although no interaction was observed, the progesterone-induced shift in time course was similar to the effects observed in Study 2, suggesting that effects that are separate form the acute effects of the parent hormone (e.g., production of progesterone metabolites) may be the driving factor in the modulation of the behavioral effects of triazolam.

The results of these studies suggest that progesterone and its metabolites modulate the behavioral effects of triazolam. This series of studies used drug discrimination to examine neuropharmacological mechanisms of action. The available evidence suggests that the behavioral effects of progesterone, independent of its primary metabolites, may occur through receptor mechanisms that are different from those of triazolam. Progesterone has been shown to modulate several receptor systems, including serotonin ($5\text{-}HT_3$), dopamine, nicotinic acetylcholine, NMDA, sigma, and oxytocin (Bullock et al, 1997; Wu et al., 1990; Rupprecht, 2003). It is unclear from existing studies the degree to which any of these neurotransmitter systems are involved in the behavioral effects of progesterone. However, a key component in the receptor based hormone-benzodiazepine interaction may be progesterone metabolites. Several studies have demonstrated that neuroactive progesterone metabolites, including allopregnanolone, pregnanolone and TH-DOC, are ligands at the $GABA_A$ receptor, and several cell culture and preclinical studies have identified these neurosteroids as a driving factor of the modulatory effects of hormones at the $GABA_A$ receptor (Lambert et al., 2009; Bertz et al., 1995; Paul & Purdy, 1992; Majewska, 1992; Majewska et al., 1986). The effects of neuroactive progesterone metabolites may have contributed to mid luteal phase potentiation of triazolam effects in Study 1, as levels of allopregnanolone are elevated for approximately 10 days during the mid luteal phase (Genazzani et al., 1998). In addition, the effects of progesterone metabolites may have also have contributed to the effects observed in Study 2, as the interaction effects occurred at times when progesterone metabolites emerge. Future studies will be required to more fully elucidate mechanisms associated with progesterone's behavioral effects and the potential role of GABA as a mechanism through with progesterone metabolites might modulate triazolam effects.

LIMITATIONS

There were several limitations to these studies that warrant mentioning. First, in Studies 1 and 3 the discriminative stimulus effects of triazolam were established without respect to menstrual cycle phase. Sample and control sessions were conducted during times when endogenous neurosteroids were at various levels, creating the possibility that the magnitude of the of the discriminative stimulus was variable throughout training. Although this may have occurred, the data do not indicate that cycle phase affected the rate at which drug discrimination was acquired or the degree of sensitivity to progesterone/cycle phase modulation in the test phase; however these studies were not powered to examine this factor. Future research should examine if sample and control sessions conducted during the mid luteal phase influence the degree of sensitivity to test doses across the cycle.

A notable limitation in Studies 2 and 3 was the use of a limited dose range of progesterone. An ideal dose range would have included a wider range of doses. The lowest dose of progesterone (100 mg), used in both studies, produced sedative-like effects on subjective and performance measures. Although much higher oral doses (600 to 1200 mg) and different routes of administration (e.g., intravenous and intramuscular) that generate higher blood levels of progesterone have been shown to increase subjective reports of sedation and fatigue (Soderpalm et al., 2004; de Wit et al., 2001; Freeman et al., 1992; van der Meer et al., 1982), 100 or 200 mg oral progesterone had not engendered sedative-like effects in previous studies (Evans & Foltin, 2006; Sofuoglu et al, 2001; 2002). A moderate-fat meal administered shortly after progesterone administration had been shown to increase oral progesterone absorption (Simon et al., 1993; Stanczyk, 1999; de Lignières, 1999), and may have increased behavioral sensitivity to these doses. Nonetheless, testing a full dose response curve of progesterone, including sub-threshold doses, would have provided a more complete assessment of the pharmacological interactions of progesterone and triazolam.

A limited dose range of triazolam was also used in each study. In particular, Study 2 tested only two active doses of triazolam, both of which showed an interaction with progesterone. Testing a sub-threshold dose (e.g., 0.06 mg/70 kg) would have been useful to determine if progesterone could modulate a lower dose of triazolam. In addition, Study 3 may have benefited from a lower training dose of triazolam. Consistent drug-like responding only occurred in the presence of the training dose (0.25 mg/70 kg).

Perhaps if a lower training dose had been used (i.e., 0.12 mg/70 kg), sensitivity to lower doses of triazolam may have occurred, thereby allowing for the detection of more subtle drug effects, particularly the effects of progesterone and progesterone modulation of drug effects. Alternatively, it may have been useful to include a higher training dose of triazolam as well. Progesterone enhanced and shifted the time course of the 0.25 mg/70 kg triazolam dose to the right. However, since this dose also served as the training dose, a ceiling effect limited the possibility of detecting any progesterone enhancement of this dose. A higher triazolam training dose would support more precise assessment of progesterone effects on the 0.25 mg/70 kg dose.

The timing of the progesterone and triazolam doses in Studies 2 and 3 produced somewhat different effects. In Study 2, progesterone was administered thirty minutes prior to triazolam administration, which positioned the peak effects of triazolam to coincide with the peak effects of progesterone metabolites, and an interaction effect was observed. In contrast, in Study 3, progesterone and triazolam were administered simultaneously, which produced concurrent peak effects of triazolam and the parent hormone progesterone, and no interaction was observed. Future studies should examine the discriminative stimulus effects of concordant peak effects of triazolam and progesterone metabolites to determine if the presence of these metabolites would modulate the discriminative stimulus effects of triazolam, which may more thoroughly address whether there are common receptor-based mechanisms of action between progesterone metabolites and triazolam.

Another limitation of these studies was the lack of pharmacokinetic data. Blood levels of triazolam, progesterone, and progesterone metabolites would have provided valuable information regarding the accuracy of menstrual cycle phase determinations, the time course of progesterone and its metabolites, the degree to which progesterone was absorbed, and the degree to which triazolam pharmacokinetics were altered in the presence of progesterone and its metabolites. Future studies should examine the manner in which blood levels of progesterone and its metabolites correlate with the sensitivity to triazolam, both across the cycle and after exogenous progesterone administration.

In addition, the population for each study was limited to pre-menopausal adult women. Moreover, in Studies 2 and 3, only women taking certain forms of oral birth

control (e.g., formulations containing a 7 day placebo phase) were included. These populations have had chronic exposure to progesterone, either through oral birth control regimens or through the mid luteal phase of the menstrual cycle. Given that the effects of repeated exposure to progesterone have been shown to change cellular signaling and developmental brain structure and function, it would be interesting to test a broader range of study populations to further understand the biological underpinnings of the hormone-benzodiazepine interaction.

Another limitation was that sample sizes were limited in each study. Although within subject design allows for detection of drug effects with relatively few participants and significant effects of both progesterone and triazolam were observed across studies, a larger sample size may have increased the ability to detect subtle drug interactions and/or individual differences in the sensitivity to progesterone and/or triazolam.

Another factor that may have influenced these results is the metabolic interaction between progesterone and triazolam. Pre-clinical research has indicated that GABAergic drugs such as benzodiazepines and ethanol (as well as non-GABAergic medications such as atypical antipsychotics) induce the production of progesterone and its metabolites (Aouad et al., 2009; Barbaccia, 2004). However, it is not clear to what degree this neurosteroid increase results in changes in drug effects.

Lastly, it is unclear the degree to which the results of these studies were influenced by the genomic effects of neurosteroids. Although the non-genomic, receptor mediated effects of progesterone are well documented, neurosteroids also have effects on genomic processes that could alter drug effects. For example, rapid changes in blood levels of neurosteroids can alter the degree of gene expression for the α_4 $GABA_A$ subunit. Rapid decreases in allopregnanolone increase gene expression, while increases in allopregnanolone decrease gene expression for the α_4 $GABA_A$ subunit (Rupprecht, 2003; Smith et al., 1998; Grobin & Morrow, 2000). Pre-clinical models (both in vitro and in vivo) suggest that expression of the α_4 subunit influences relative sensitivity to benzodiazepines, with increased gene transcription leading to decreased sensitivity to benzodiazepines and decreased gene expression increasing sensitivity to benzodiazepines (Smith et al., 1998; Grobin & Morrow, 2000). Although the time course of these genomic effects in humans is unclear, pre-clinical models have demonstrated changes in $GABA_A$-mediated seizure susceptibility 24 hours after neurosteroid

manipulations (Smith et al., 1998). Additional research is necessary to determine the the time course of genomic modulation of $GABA_A$ receptor composition in humans.

IMPLICATIONS

Despite these limitations, these series of studies established that progesterone plays a role in the behavioral effects of triazolam. To build on these results, future research should further examine the mechanism of action of progesterone at the $GABA_A$ receptor. Although the behavioral effects of neurosteroids are thought to result from their action at steroid-specific site on the $GABA_A$ receptor, this effect has been difficult to establish, as there are no competitive antagonists available that block the action of $GABA_A$ modulators that act at steroid-specific binding sites or to block the metabolism of progesterone, thereby allowing for the independent examination of the effects of progesterone and its metabolites. However, pre-clinical research examining the discriminative stimulus effects of neurosteroids, benzodiazepines and negative $GABA_A$ modulators provide evidence for a separate binding site for neurosteroids and benzodiazepines at the $GABA_A$ receptor. For example, pre-clinical models have demonstrated that pregnanolone, a neuroactive progesterone metabolite, substitutes for the discriminative stimulus effects of midazolam; however certain negative $GABA_A$ modulators (β-CCE and β-CCM) block this substitution while leaving the discriminative stimulus effects of midazolam intact. Alternatively, other antagonists/negative modulators (flumazenil, Ro-1545-13) leave pregnanolone substitution intact, but block the discriminative stimulus effects of midazolam (McMahon & France, 2005b; McMahon et al., 2001). This selective blockage of neurosteroid and benzodiazepine effects indicates that although their mechanisms of action at the $GABA_A$ receptor are similar (as evidenced by the substitution profile), the exact receptor-level mechanisms are distinguishable and likely occur through slightly different mechanisms. Future research should examine the discriminative stimulus effects of allopregnanolone, alone and in combination with a benzodiazepine in women and determine if negative $GABA_A$ modulators act in a similar manner to selectively block the discriminative stimulus effects of each compound, in order to further clarify the neurobiological basis of the interaction in humans.

Although the pre-clinical research has suggested GABAergic mechanism for neurosteroids, the data from these studies, specifically Study 3, indicate that progesterone effects were not exclusively mediated by its action at the $GABA_A$ receptor.

The neurobiological basis of the sedative-like effects of progesterone are unclear, as progesterone engendered subjective and performance effects, but did not modulate or substitute for the discriminative stimulus effects of triazolam. As progesterone has also been shown to modulate several other neurotransmitter systems (Bullock et al, 1997; Wu et al., 1990; Rupprecht, 2003), future research should examine the degree to which progesterone substitutes for the discriminative stimulus effects of drugs acting at serotonin ($5\text{-}HT_3$), dopamine, nicotinic acetylcholine, NMDA, sigma, and oxytocin receptors. Alternatively, applying medications that act as antagonists at these receptors, as well as selective negative $GABA_A$ modulators, in combination with progesterone, could also help to determine the neurobiological mechanisms that contribute to its behavioral effects.

Taken together, the results of these studies have clinical importance, as they demonstrate that drug effects can be influenced by ovarian hormones. This information is important when considering women's health, as the effects of centrally acting medications may not have static effects across the menstrual cycle, during adolescence, or during menopause, as these all reflect times when hormone levels are rapidly changing. Knowledge of this effect has led to cycle-based modifications in GABAergic medication regimens for women being treated for epilepsy (Reddy, 2009; Herzog et al., 2009; Bäckström, 1976). In addition, doses of certain types of anaesthesia medications are also titrated based on levels of endogenous neurosteroids (Erden et al., 2005). Future research should determine if dose modifications might be necessary for other GABAergic medications as well.

Importantly, additional research is also necessary to determine if menstrual cycle changes influence drug abuse liability in women, as it is not known if the reinforcing effects of certain drugs may change as a function of menstrual cycle phase. Variation in levels of endogenous neurosteroids, both within and between individuals, may also occasion individual differences in the effects of drugs of abuse. Rapidly increasing levels of neurosteroids (i.e., beginning of the luteal phase, during female adolescence), or abrupt declines in neurosteroid levels (i.e., late luteal phase, peri-menopause and menopause) may enhance or attenuate acute pharmacological effects, thereby potentially altering the functional effects of drugs. Recognizing the degree to which hormone variations influence drug effects may help identify gender differences in drug abuse liability.

Hormonal modulation of drug effects may be an important factor in men's sensitivity to drug effects as well. Although hormonal milieu is not typically thought to contribute differences in acute drug effects in men, there are data suggesting that exogenous neurosteroids have similar subjective effects in men and women and similar discriminative stimulus effects in male and female animals (Grant et al., 2008; Söderpalm et al., 2004). It is not clear if an interaction between exogenous neurosteroids and GABAergic drugs would occur in men, but future research should examine this possibility, as it would provide insight into the mechanisms that occasion the interaction and would clarify if developmental brain structure unique to each sex or if chronic exposure to neuroactive steroids (via the menstrual cycle phase) are necessary mediators in the interaction. This information would also inform men's health and susceptibility to drug use. For example, it is unclear the degree to which men with elevated levels of endogenous neurosteroids (occurring through natural variations or in disease states) may display sensitivity to GABAergic drug effects.

The manner in which progesterone interacts with GABAergic medications in a variety of populations becomes increasingly important as progesterone becomes more popular as a prescribed therapeutic. Progesterone is currently prescribed to women for hormone replacement therapy, infertility, amenorrhea and epilepsy (Mahmud, 2009; Check, 2009; Whitehead et al., 1990; Reddy & Rogawski, 2009). In addition, clinical trials have been conducted using chronic progesterone therapy as a pharmacotherapeutic for the treatment of cocaine abuse in men (Sofuoglu et al., 2007). Current clinical trials are also being conducted to determine if very large doses of intravenous progesterone can decrease the neuronal damage associated with traumatic brain injury (Wright et al., 2007). Endogenous levels of neurosteroids are also taken into account when formulating drug regimens for women who are diagnosed with epilepsy, specifically catamenial epilepsy, a condition in which hormone levels are associated with risk of seizure. Neurosteroids act as anti-epileptics and rapid decreases in these hormones decrease seizure threshold (Biagini et al., 2010). Doses of anti-epileptic medications are often adjusted to accommodate fluctuations of endogenous hormones, with increases in medication doses occurring during times when progesterone levels are minimal (follicular phase, late luteal phase) to reduce the possibility of seizures (Biagini et al., 2010). In addition, new therapies are being developed in which exogenous neurosteroids (progesterone, allopregnanolone and synthetic derivates of these hormones) are administered to help control the frequency of catamenial seizures (Reddy

& Rogawski, 2009). Information regarding the degree to which progesterone modulates GABAergic function in both men and women and the subsequent interaction with benzodiazepine and barbiturate medications and alcohol may become increasingly important as these lines of treatment develop.

Taken together, data from these and similar studies will be helpful in the identification of individual differences in drug effects and will assist in formulating of gender-specific prevention or treatment techniques.

Appendix A. Means and Standard Error Values for Measures Collected in Study 1

		EARLY FOLLICULAR PHASE								MID LUTEAL PHASE							
DRUG DISCRIMINATION																	
Test Phase		TRIAZOLAM DOSE (mg/70 kg)								TRIAZOLAM DOSE (mg/70 kg)							
	TIME	0.00		0.06		0.12		0.25		0.00		0.06		0.12		0.25	
	30	26.16	(15.70)	34.32	(16.12)	42.34	(17.56)	34.73	(17.11)	31.15	(11.94)	35.57	(15.22)	41.98	(17.73)	72.94	(13.32)
	60	41.24	(18.29)	39.62	(18.26)	33.57	(19.32)	66.58	(19.25)	14.29	(15.43)	28.57	(16.47)	58.86	(20.28)	61.38	(20.08)
	90	42.86	(21.82)	31.22	(16.70)	45.37	(20.39)	78.44	(16.11)	21.43	(16.06)	18.25	(15.37)	80.61	(14.93)	76.19	(17.06)
	120	42.86	(21.82)	24.76	(17.18)	40.38	(20.08)	100.00	(0.0)	14.29	(15.43)	14.30	(12.52)	85.71	(14.82)	85.71	(15.43)
	150	42.86	(21.82)	25.20	(17.50)	43.94	(20.63)	100.00	(0.0)	14.29	(15.43)	17.12	(14.69)	85.71	(14.82)	87.01	(14.03)
SELF-REPORT MEASURES																	
VAS		0.00		0.06		0.12		0.25		0.00		0.06		0.12		0.25	
Stimulated	0	0.86	(0.37)	1.71	(1.01)	1.57	(0.96)	1.14	(0.50)	0.86	(0.28)	0.93	(0.47)	1.71	(1.41)	0.57	(0.40)
	30	1.14	(0.60)	2.64	(1.46)	3.29	(2.48)	1.57	(1.02)	1.14	(0.55)	2.50	(1.16)	1.71	(1.49)	1.00	(0.75)
	60	1.00	(0.58)	2.79	(1.57)	3.86	(3.46)	11.00	(9.86)	1.57	(0.70)	4.79	(2.79)	2.86	(2.25)	1.14	(0.55)
	90	1.43	(0.46)	2.86	(1.71)	4.36	(2.47)	10.00	(7.71)	2.43	(1.43)	2.29	(1.38)	5.64	(4.07)	1.14	(0.68)
	120	1.29	(0.73)	2.00	(1.39)	3.79	(2.02)	6.57	(4.36)	3.29	(1.90)	2.29	(1.81)	4.00	(3.19)	1.29	(0.70)
	150	1.43	(0.62)	2.50	(1.15)	2.79	(1.15)	8.14	(5.33)	3.43	(2.64)	1.57	(0.61)	2.57	(1.63)	2.71	(1.31)
Sedated	0	1.14	(0.37)	1.14	(0.48)	1.14	(0.35)	0.71	(0.31)	1.14	(0.44)	0.93	(0.41)	0.79	(0.54)	1.29	(0.45)
	30	5.14	(3.0)	5.07	(4.68)	4.71	(3.35)	1.29	(0.90)	3.29	(1.61)	2.50	(1.12)	2.79	(1.70)	9.57	(7.56)
	60	5.43	(2.92)	7.21	(4.68)	9.07	(7.58)	28.86	(14.92)	6.00	(3.92)	7.14	(4.04)	14.93	(1.70)	12.57	(9.30)
	90	12.86	(11.09)	9.36	(4.36)	8.36	(6.08)	31.43	(13.87)	7.00	(5.14)	8.14	(5.21)	20.00	(8.56)	30.14	(16.86)
	120	15.71	(13.66)	5.93	(6.20)	9.79	(7.01)	31.00	(12.95)	7.14	(5.67)	6.50	(6.18)	22.86	(7.33)	32.57	(15.10)
	150	12.43	(11.28)	6.21	(4.89)	9.29	(7.07)	32.00	(11.83)	6.00	(5.09)	7.29	(8.08)	12.21	(8.82)	31.71	(15.79)
Anxious	0	3.86	(2.15)	3.43	(2.21)	4.29	(3.63)	2.86	(1.52)	2.14	(1.03)	1.29	(0.53)	6.57	(3.10)	6.43	(3.09)
	30	3.43	(2.15)	5.64	(3.08)	3.86	(2.15)	3.43	(1.80)	1.29	(0.34)	3.50	(3.23)	4.29	(2.10)	1.14	(0.66)
	60	4.86	(2.76)	3.36	(1.85)	6.00	(4.40)	7.71	(4.96)	6.86	(4.34)	2.64	(1.66)	5.21	(2.93)	3.86	(2.15)
	90	3.14	(2.33)	2.07	(1.58)	9.07	(4.46)	6.29	(4.69)	5.43	(2.82)	2.21	(0.90)	9.36	(5.96)	5.86	(4.72)
	120	5.71	(4.01)	1.36	(0.64)	7.57	(4.15)	5.57	(2.83)	4.00	(2.28)	3.21	(1.12)	3.79	(2.27)	3.86	(1.73)
	150	4.71	(2.77)	1.36	(0.53)	6.64	(5.30)	6.71	(3.07)	7.14	(4.61)	3.36	(3.04)	2.43	(1.20)	9.86	(5.81)
High	0	0.86	(0.43)	1.07	(0.49)	0.71	(0.35)	0.86	(0.38)	1.00	(0.35)	1.00	(0.34)	1.29	(0.53)	1.00	(0.54)
	30	2.71	(1.17)	2.14	(0.98)	3.00	(1.66)	1.14	(0.52)	1.14	(0.52)	1.50	(0.50)	2.43	(1.43)	2.00	(0.82)
	60	5.29	(1.32)	2.14	(0.77)	4.36	(3.88)	13.14	(8.24)	2.86	(1.03)	2.50	(1.14)	3.79	(1.77)	3.29	(1.60)
	90	3.57	(1.27)	3.50	(1.71)	3.00	(1.29)	18.71	(8.98)	3.29	(1.75)	1.50	(0.58)	9.86	(4.0)	4.29	(1.54)
	120	2.29	(0.57)	3.07	(1.74)	2.86	(1.98)	19.00	(9.50)	1.00	(0.35)	1.14	(0.46)	12.71	(8.26)	5.29	(1.81)
	150	2.29	(0.57)	1.86	(0.76)	2.86	(1.84)	18.86	(11.22)	1.14	(0.52)	1.14	(0.50)	6.86	(6.53)	13.71	(6.14)
Confident	0	47.29	(17.56)	49.79	(16.79)	52.21	(17.09)	41.86	(17.86)	49.29	(17.16)	49.14	(16.66)	49.86	(16.68)	47.43	(17.56)
	30	29.71	(9.85)	31.57	(7.36)	37.36	(8.68)	39.14	(13.07)	33.14	(8.72)	27.36	(9.47)	33.93	(11.52)	23.00	(5.02)
	60	36.86	(10.03)	36.07	(9.53)	57.79	(9.55)	43.00	(12.69)	44.71	(13.03)	39.64	(8.64)	56.86	(7.70)	43.71	(10.36)
	90	53.14	(13.11)	44.79	(9.52)	60.50	(10.35)	57.71	(12.68)	57.86	(11.89)	50.50	(12.91)	52.21	(6.96)	51.43	(10.87)
	120	57.00	(13.72)	57.00	(10.91)	65.71	(11.79)	64.43	(14.66)	68.00	(9.55)	56.93	(12.76)	62.43	(10.29)	65.14	(10.03)
	150	61.43	(13.32)	61.86	(11.45)	69.71	(12.07)	69.57	(13.29)	73.00	(10.86)	63.57	(13.48)	66.14	(10.12)	67.29	(12.08)
Hungry	0	30.14	(9.19)	44.64	(8.12)	34.43	(10.06)	36.57	(7.93)	44.43	(10.47)	36.14	(12.52)	40.93	(12.52)	49.29	(12.86)
	30	10.29	(5.32)	14.14	(5.19)	11.86	(4.04)	14.57	(4.58)	15.29	(4.33)	13.29	(4.56)	12.43	(5.06)	11.14	(3.83)
	60	19.86	(4.24)	20.57	(5.85)	19.86	(7.05)	22.57	(4.74)	13.43	(3.04)	15.86	(5.94)	19.21	(6.17)	14.71	(3.31)
	90	18.29	(5.16)	30.14	(8.06)	26.64	(7.94)	33.86	(4.15)	27.29	(11.08)	29.00	(5.76)	25.29	(7.26)	27.43	(6.88)
	120	27.00	(6.75)	31.86	(6.07)	33.36	(8.21)	38.00	(4.24)	39.14	(8.86)	40.29	(7.82)	33.21	(9.10)	28.86	(6.66)
	150	37.14	(4.63)	45.50	(9.17)	40.29	(9.92)	39.00	(4.33)	46.29	(7.40)	43.21	(9.59)	44.43	(7.71)	39.00	(5.34)
Thirsty	0	31.57	(10.91)	35.57	(11.73)	31.71	(11.76)	34.29	(12.07)	45.00	(13.61)	34.50	(11.76)	40.50	(12.62)	47.00	(12.61)
	30	19.00	(8.29)	19.07	(9.27)	20.79	(9.36)	23.86	(10.60)	27.00	(10.46)	26.07	(9.85)	23.14	(7.19)	27.00	(9.32)
	60	25.00	(8.65)	23.79	(9.27)	24.21	(8.19)	31.86	(10.11)	31.57	(12.41)	25.43	(10.10)	23.57	(7.19)	25.71	(10.07)
	90	26.86	(11.48)	31.36	(12.02)	29.14	(9.04)	37.57	(10.99)	40.14	(13.66)	32.57	(9.88)	28.93	(7.86)	33.29	(10.51)
	120	33.29	(11.94)	30.07	(9.45)	35.29	(11.55)	39.71	(12.87)	37.71	(14.35)	32.86	(11.13)	32.14	(9.38)	35.71	(8.14)
	150	36.86	(9.82)	40.93	(11.56)	38.86	(12.46)	35.71	(10.59)	44.43	(13.14)	38.00	(12.27)	41.43	(10.79)	38.00	(11.21)
Drug Effect	0	0.86	(0.44)	0.86	(0.31)	0.86	(0.60)	0.86	(0.50)	0.71	(0.31)	1.29	(0.63)	0.71	(0.49)	1.00	(0.47)
	30	7.86	(3.72)	9.14	(3.96)	8.29	(4.53)	3.57	(2.62)	7.57	(4.72)	9.86	(5.13)	5.86	(3.96)	11.00	(6.44)
	60	4.43	(2.85)	10.57	(4.85)	12.43	(9.82)	34.57	(14.24)	6.14	(4.41)	10.93	(4.60)	18.00	(8.62)	16.00	(9.27)
	90	13.57	(10.71)	11.36	(5.13)	16.21	(9.72)	40.43	(14.12)	13.29	(9.78)	10.93	(5.98)	30.29	(10.40)	31.14	(16.55)
	120	17.43	(12.22)	8.36	(6.45)	19.79	(11.37)	42.57	(12.27)	10.14	(7.54)	10.14	(6.85)	25.43	(12.07)	39.14	(14.80)
	150	18.14	(14.54)	8.93	(6.44)	14.00	(9.68)	44.86	(15.31)	11.86	(7.50)	6.50	(8.41)	18.21	(9.86)	36.71	(15.41)
Like Drug Effect	0	1.00	(0.58)	1.64	(0.90)	4.29	(5.06)	0.29	(0.20)	1.14	(0.55)	1.21	(0.60)	1.29	(0.74)	0.86	(0.37)
	30	2.86	(1.52)	4.71	(3.16)	2.79	(1.58)	1.29	(0.73)	3.00	(1.53)	4.29	(3.41)	1.43	(0.71)	4.43	(3.89)
	60	2.86	(1.69)	4.07	(3.16)	2.79	(2.24)	15.43	(8.30)	2.86	(1.44)	7.36	(4.75)	5.21	(0.71)	5.43	(4.10)
	90	13.29	(12.03)	5.57	(2.78)	5.36	(4.39)	24.14	(15.54)	4.71	(3.86)	5.64	(4.62)	7.29	(3.33)	21.14	(13.82)
	120	13.43	(9.90)	4.93	(2.73)	6.29	(5.16)	19.71	(13.96)	4.71	(3.53)	4.71	(3.48)	9.00	(3.19)	9.57	(4.27)
	150	15.86	(13.98)	3.36	(2.67)	6.07	(5.49)	25.71	(16.84)	1.57	(0.85)	3.57	(3.29)	8.71	(5.89)	8.86	(3.82)
ARS																	
Stimulant	0	10.00	(1.37)	8.71	(1.19)	10.43	(1.53)	9.86	(1.52)	10.57	(1.91)	10.07	(1.71)	9.64	(2.15)	8.14	(1.21)
	30	8.00	(1.29)	6.64	(1.15)	8.64	(1.56)	8.29	(1.39)	8.86	(2.37)	8.57	(1.77)	7.36	(1.35)	6.00	(0.94)
	60	6.43	(0.97)	6.50	(1.28)	8.93	(1.68)	8.00	(1.72)	8.71	(2.26)	7.93	(1.85)	6.57	(1.38)	5.00	(0.82)
	90	7.43	(1.10)	6.57	(3.25)	8.29	(1.64)	7.71	(1.37)	8.71	(2.16)	3.22	(2.18)	6.36	(1.27)	5.71	(1.37)
	120	7.57	(1.18)	6.64	(0.84)	7.79	(1.63)	7.14	(1.52)	9.71	(2.42)	2.32	(1.99)	7.07	(1.66)	4.43	(1.18)
	150	7.71	(1.02)	6.71	(1.44)	9.07	(1.62)	8.29	(1.78)	9.29	(2.26)	2.59	(1.74)	8.14	(1.75)	5.43	(0.97)
Sedative	0	3.86	(1.07)	4.57	(1.57)	3.71	(1.50)	3.57	(0.91)	2.86	(0.90)	3.57	(1.13)	3.86	(1.06)	3.14	(1.54)
	30	6.57	(2.60)	5.64	(1.34)	5.71	(2.78)	4.57	(1.37)	4.29	(0.90)	4.79	(1.39)	5.07	(1.07)	6.57	(1.0)
	60	7.00	(1.87)	7.64	(1.52)	6.50	(2.87)	8.14	(1.85)	4.57	(1.0)	4.86	(1.67)	6.93	(1.17)	10.00	(2.38)
	90	6.43	(2.37)	6.43	(1.39)	6.43	(1.65)	10.43	(2.67)	5.86	(1.16)	5.57	(2.04)	7.21	(1.42)	11.43	(3.13)
	120	7.00	(2.27)	6.57	(1.41)	6.64	(1.68)	11.14	(2.07)	5.14	(1.14)	4.71	(1.39)	8.93	(2.43)	12.57	(2.63)
	150	7.29	(2.85)	6.14	(1.04)	5.50	(1.40)	11.57	(2.50)	4.71	(0.77)	4.86	(1.62)	7.43	(1.93)	11.14	(2.18)

		EARLY FOLLICULAR PHASE								MID LUTEAL PHASE							
PERFORMANCE MEASURES		TRIAZOLAM DOSE (mg/70 kg)								TRIAZOLAM DOSE (mg/70 kg)							
DSST		**0.00**		**0.06**		**0.12**		**0.25**		**0.00**		**0.06**		**0.12**		**0.25**	
Trial Rate	0	0.67	(0.04)	0.67	(0.04)	0.66	(0.05)	0.67	(0.04)	0.67	(0.04)	0.68	(0.04)	0.68	(0.04)	0.69	(0.04)
	30	0.67	(0.04)	0.68	(0.04)	0.66	(0.04)	0.67	(0.04)	0.68	(0.04)	0.68	(0.04)	0.67	(0.04)	0.69	(0.04)
	60	0.68	(0.04)	0.66	(0.04)	0.67	(0.04)	0.65	(0.04)	0.66	(0.04)	0.67	(0.04)	0.66	(0.04)	0.67	(0.04)
	90	0.66	(0.04)	0.66	(0.04)	0.66	(0.04)	0.64	(0.04)	0.68	(0.04)	0.66	(0.04)	0.66	(0.04)	0.65	(0.05)
	120	0.67	(0.04)	0.66	(0.04)	0.66	(0.04)	0.63	(0.04)	0.68	(0.04)	0.67	(0.04)	0.66	(0.04)	0.65	(0.04)
	150	0.68	(0.04)	0.67	(0.04)	0.66	(0.04)	0.64	(0.04)	0.67	(0.04)	0.66	(0.04)	0.66	(0.04)	0.65	(0.04)
Correct	0	0.65	(0.04)	0.65	(0.04)	0.65	(0.05)	0.66	(0.04)	0.65	(0.04)	0.66	(0.04)	0.66	(0.04)	0.67	(0.04)
	30	0.65	(0.04)	0.65	(0.03)	0.65	(0.04)	0.65	(0.04)	0.66	(0.03)	0.67	(0.04)	0.65	(0.04)	0.67	(0.04)
	60	0.65	(0.03)	0.64	(0.03)	0.65	(0.04)	0.63	(0.04)	0.64	(0.04)	0.65	(0.04)	0.65	(0.04)	0.65	(0.04)
	90	0.63	(0.04)	0.64	(0.04)	0.64	(0.04)	0.62	(0.04)	0.66	(0.04)	0.64	(0.04)	0.64	(0.04)	0.64	(0.05)
	120	0.66	(0.04)	0.65	(0.04)	0.64	(0.04)	0.60	(0.04)	0.66	(0.04)	0.66	(0.04)	0.64	(0.04)	0.62	(0.04)
	150	0.66	(0.04)	0.65	(0.04)	0.63	(0.04)	0.62	(0.04)	0.66	(0.04)	0.65	(0.04)	0.64	(0.04)	0.63	(0.03)
% Incorrect	0	0.02	(0.01)	0.02	(0.0)	0.01	(0.0)	0.01	(0.01)	0.01	(0.0)	0.01	(0.01)	0.01	(0.0)	0.02	(0.01)
	30	0.02	(0.01)	0.03	(0.01)	0.01	(0.0)	0.01	(0.0)	0.01	(0.01)	0.01	(0.01)	0.03	(0.01)	0.01	(0.0)
	60	0.02	(0.01)	0.02	(0.0)	0.02	(0.01)	0.02	(0.01)	0.02	(0.01)	0.02	(0.0)	0.02	(0.0)	0.02	(0.01)
	90	0.03	(0.0)	0.02	(0.01)	0.02	(0.01)	0.02	(0.01)	0.02	(0.01)	0.02	(0.0)	0.01	(0.0)	0.02	(0.0)
	120	0.01	(0.0)	0.02	(0.01)	0.02	(0.01)	0.02	(0.01)	0.02	(0.01)	0.01	(0.0)	0.02	(0.0)	0.02	(0.01)
	150	0.02	(0.01)	0.02	(0.01)	0.03	(0.01)	0.02	(0.0)	0.02	(0.01)	0.02	(0.0)	0.02	(0.0)	0.03	(0.01)
% Correct	0	0.97	(0.01)	0.97	(0.01)	0.98	(0.01)	0.98	(0.01)	0.98	(0.0)	0.98	(0.01)	0.98	(0.01)	0.97	(0.01)
	30	0.97	(0.01)	0.96	(0.02)	0.98	(0.01)	0.98	(0.01)	0.98	(0.01)	0.99	(0.01)	0.96	(0.01)	0.98	(0.01)
	60	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.96	(0.01)
	90	0.96	(0.01)	0.97	(0.01)	0.97	(0.01)	0.97	(0.01)	0.98	(0.01)	0.97	(0.01)	0.98	(0.01)	0.98	(0.01)
	120	0.98	(0.01)	0.97	(0.01)	0.97	(0.01)	0.96	(0.01)	0.97	(0.01)	0.98	(0.01)	0.97	(0.01)	0.96	(0.01)
	150	0.98	(0.01)	0.97	(0.01)	0.96	(0.02)	0.96	(0.01)	0.98	(0.01)	0.97	(0.01)	0.98	(0.01)	0.96	(0.01)
CARDIOVASCULAR MEASURES																	
Heart Rate		**0.00**		**0.06**		**0.12**		**0.25**		**0.00**		**0.06**		**0.12**		**0.25**	
	0	72.71	(2.49)	70.71	(2.96)	69.93	(2.71)	69.71	(2.47)	73.71	(3.07)	74.00	(2.90)	74.21	(3.27)	73.14	(3.22)
	30	71.57	(1.82)	76.79	(2.80)	72.79	(2.06)	76.43	(1.61)	78.57	(2.89)	77.36	(2.51)	76.07	(2.84)	78.43	(3.29)
	60	73.71	(2.69)	76.57	(3.10)	76.36	(2.93)	74.71	(2.13)	75.71	(2.67)	75.64	(2.19)	78.14	(3.21)	78.71	(2.0)
	90	68.29	(2.78)	73.29	(3.10)	74.57	(3.33)	73.86	(3.52)	75.86	(3.20)	76.14	(2.72)	74.36	(2.98)	78.00	(3.18)
	120	69.57	(3.03)	70.86	(2.71)	71.36	(2.10)	74.29	(2.58)	73.43	(3.81)	72.71	(2.77)	72.79	(2.75)	81.00	(3.21)
	150	70.14	(4.45)	69.50	(2.89)	68.64	(2.84)	70.57	(2.65)	71.29	(3.08)	72.29	(2.70)	71.93	(3.34)	77.00	(3.40)
Systolic BP	0	113.00	(3.62)	114.14	(4.35)	115.93	(4.0)	112.86	(3.36)	115.57	(3.45)	116.14	(4.02)	115.93	(6.01)	112.14	(4.62)
	30	121.86	(6.0)	113.79	(3.69)	118.86	(4.81)	109.43	(2.32)	113.86	(3.05)	117.21	(3.28)	115.14	(4.97)	115.14	(3.16)
	60	116.71	(3.98)	115.36	(3.69)	114.71	(4.05)	112.14	(3.07)	114.29	(3.07)	116.07	(4.30)	116.36	(4.97)	113.86	(3.47)
	90	115.86	(5.31)	116.43	(3.59)	115.57	(3.84)	114.57	(3.13)	114.43	(2.80)	119.07	(3.26)	114.07	(5.23)	110.29	(6.89)
	120	115.43	(3.70)	116.36	(3.77)	116.86	(3.46)	116.43	(4.85)	114.57	(3.99)	119.36	(2.63)	111.36	(4.89)	113.43	(3.60)
	150	114.86	(4.42)	116.50	(4.09)	111.00	(6.94)	116.57	(3.19)	114.43	(3.64)	119.07	(3.71)	116.93	(4.44)	117.00	(5.26)
Diastolic BP	0	75.14	(2.24)	71.14	(3.59)	68.71	(2.28)	73.43	(2.10)	64.14	(4.46)	67.29	(3.09)	65.29	(2.40)	67.29	(3.0)
	30	67.57	(4.56)	68.86	(2.27)	62.93	(3.03)	71.43	(2.52)	69.29	(2.65)	67.07	(3.01)	64.71	(2.33)	70.00	(1.93)
	60	70.00	(1.63)	67.57	(2.40)	70.00	(3.08)	75.43	(1.51)	64.86	(1.60)	68.86	(1.62)	65.00	(2.78)	65.00	(2.32)
	90	66.57	(3.17)	68.57	(1.81)	69.57	(2.38)	72.57	(1.93)	66.43	(2.45)	65.36	(2.84)	64.64	(2.22)	65.00	(2.26)
	120	70.00	(2.19)	70.71	(2.07)	69.29	(2.06)	73.00	(2.48)	68.00	(1.34)	67.07	(3.60)	66.57	(2.51)	65.14	(1.86)
	150	71.57	(1.95)	72.57	(4.11)	67.29	(3.14)	73.29	(1.13)	73.29	(3.26)	73.21	(1.97)	70.07	(3.0)	68.43	(3.21)
MAP	0	89.29	(3.32)	88.57	(4.72)	82.64	(2.46)	88.71	(2.64)	81.29	(5.83)	82.79	(3.96)	81.21	(3.94)	84.71	(4.47)
	30	83.29	(5.34)	84.86	(3.11)	78.29	(3.92)	83.29	(3.53)	85.57	(4.10)	84.00	(4.24)	80.64	(3.12)	87.57	(2.83)
	60	84.57	(2.05)	82.36	(1.78)	84.14	(4.10)	88.71	(2.02)	80.43	(3.34)	82.00	(1.66)	80.00	(2.91)	80.71	(3.31)
	90	79.43	(3.52)	85.00	(2.66)	83.36	(2.61)	85.71	(2.29)	81.86	(2.97)	80.57	(3.41)	79.50	(2.80)	81.14	(2.95)
	120	88.14	(3.75)	85.79	(2.87)	85.14	(3.14)	86.71	(2.34)	86.00	(1.33)	84.64	(4.10)	81.64	(3.50)	78.71	(1.50)
	150	88.57	(1.60)	86.79	(5.09)	80.79	(4.90)	87.43	(1.71)	86.43	(3.93)	89.50	(2.72)	85.71	(3.63)	84.86	(2.96)

Appendix B. Means and Standard Error Values for Measures Collected in Study 2

SELF-REPORT MEASURES		0 mg PROGESTERONE						100 mg PROGESTERONE						200 mg PROGESTERONE					
VAS	TIME	0.00		0.12		0.25		0.00		0.12		0.25		0.00		0.12		0.25	
Stimulated	0	8.73	(2.84)	12.18	(4.53)	8.55	(3.89)	10.73	(4.02)	15.82	(6.40)	12.73	(5.40)	7.45	(2.88)	10.00	(3.32)	7.91	(3.86)
	30	7.82	(2.74)	8.64	(2.32)	13.18	(4.24)	10.09	(3.34)	21.36	(6.72)	14.91	(4.14)	15.18	(5.40)	13.45	(4.45)	18.64	(8.87)
	60	9.45	(3.40)	5.36	(2.98)	8.45	(3.41)	18.64	(3.34)	15.00	(6.24)	11.45	(4.13)	18.55	(5.39)	10.00	(3.33)	13.91	(6.08)
	90	13.09	(4.75)	5.00	(1.84)	10.09	(3.66)	10.09	(6.51)	13.82	(5.88)	7.82	(3.70)	15.64	(6.38)	9.09	(4.38)	18.27	(5.87)
	120	9.00	(3.39)	3.36	(1.73)	12.45	(5.13)	7.73	(2.53)	12.91	(7.23)	12.82	(4.28)	9.00	(2.82)	8.27	(3.38)	16.36	(4.50)
	150	7.27	(2.81)	4.73	(2.15)	11.09	(4.60)	8.64	(3.12)	9.09	(3.57)	10.55	(4.20)	7.55	(2.89)	10.00	(3.96)	12.91	(5.11)
Sedated	0	4.36	(2.66)	2.55	(1.53)	8.45	(5.08)	5.00	(2.65)	3.09	(1.82)	4.00	(2.12)	3.27	(1.61)	5.27	(2.65)	3.45	(1.40)
	30	16.73	(8.36)	7.64	(2.79)	16.09	(6.19)	17.36	(6.41)	23.36	(8.35)	10.64	(3.24)	24.36	(7.85)	23.73	(6.51)	20.36	(7.50)
	60	14.00	(6.37)	5.73	(2.49)	16.27	(5.10)	21.82	(6.97)	21.36	(8.83)	18.36	(6.11)	27.18	(7.67)	18.91	(6.18)	19.45	(7.17)
	90	10.09	(3.92)	4.00	(2.16)	14.55	(5.33)	17.55	(6.43)	23.00	(9.24)	13.91	(6.51)	21.55	(6.91)	23.91	(9.0)	24.27	(5.76)
	120	10.09	(4.78)	5.91	(2.38)	21.82	(9.75)	5.64	(2.68)	17.00	(7.55)	28.00	(8.15)	15.82	(6.39)	20.82	(7.81)	28.27	(8.98)
	150	10.91	(5.35)	13.00	(5.45)	18.27	(5.57)	7.36	(3.43)	17.64	(7.92)	25.27	(7.46)	11.09	(5.86)	16.45	(6.78)	22.36	(6.45)
Stressed	0	23.55	(7.94)	13.73	(8.20)	10.55	(3.49)	11.55	(5.18)	14.91	(5.71)	13.36	(5.57)	14.91	(6.12)	10.45	(4.60)	10.00	(4.98)
	30	17.36	(7.93)	5.55	(2.80)	7.55	(3.42)	12.00	(6.25)	6.45	(3.31)	9.00	(4.56)	7.36	(4.02)	8.55	(4.55)	6.73	(3.57)
	60	17.36	(8.64)	4.82	(2.08)	6.55	(2.94)	11.00	(5.79)	4.45	(2.42)	5.91	(3.13)	8.27	(4.16)	7.18	(4.13)	7.64	(4.25)
	90	8.27	(4.96)	4.27	(2.18)	5.09	(2.89)	12.27	(5.65)	8.64	(4.10)	7.00	(3.20)	7.91	(4.45)	8.82	(4.73)	8.91	(3.89)
	120	18.91	(7.95)	6.27	(3.90)	5.55	(2.84)	17.00	(7.69)	6.36	(3.36)	4.64	(2.50)	6.00	(3.0)	5.91	(2.51)	5.91	(2.96)
	150	10.00	(5.49)	4.09	(2.32)	4.73	(2.42)	13.55	(6.48)	6.18	(2.79)	5.73	(3.07)	6.09	(3.53)	8.09	(4.03)	8.09	(2.78)
Anxious	0	19.45	(6.88)	11.73	(6.58)	10.64	(4.18)	10.55	(3.45)	14.73	(5.45)	11.18	(4.09)	10.18	(5.15)	9.55	(3.19)	12.36	(5.16)
	30	6.36	(2.97)	12.18	(5.74)	10.45	(4.64)	8.00	(2.95)	10.36	(5.24)	5.73	(3.15)	7.82	(3.18)	8.36	(3.53)	10.45	(4.58)
	60	12.82	(5.48)	14.55	(5.31)	10.91	(4.70)	8.82	(3.74)	4.09	(1.80)	7.45	(2.95)	6.91	(2.83)	8.36	(3.25)	11.45	(4.58)
	90	13.45	(6.26)	17.45	(6.58)	10.27	(4.04)	11.55	(4.27)	8.73	(5.61)	6.27	(3.37)	10.55	(5.50)	12.55	(6.03)	10.45	(4.21)
	120	14.00	(6.11)	16.82	(6.05)	12.27	(7.31)	17.09	(7.99)	11.45	(3.94)	8.82	(3.75)	10.27	(6.16)	12.36	(5.88)	12.36	(2.94)
	150	16.91	(7.73)	18.09	(6.93)	8.64	(4.04)	16.91	(7.55)	12.64	(4.46)	11.45	(4.56)	9.82	(5.60)	5.73	(2.31)	5.73	(6.14)
Nervous	0	6.27	(3.47)	7.73	(6.11)	5.73	(2.43)	7.36	(2.94)	5.27	(2.71)	3.91	(2.44)	5.91	(2.97)	7.27	(2.95)	6.45	(3.32)
	30	6.91	(3.64)	3.64	(1.69)	7.36	(3.02)	6.55	(2.64)	4.00	(2.22)	7.18	(3.57)	5.36	(2.84)	5.73	(2.81)	5.00	(2.08)
	60	6.82	(3.43)	4.55	(2.21)	4.82	(2.31)	6.73	(2.96)	3.55	(1.90)	5.09	(2.59)	3.64	(2.31)	4.82	(2.51)	6.64	(3.33)
	90	7.27	(3.52)	4.27	(2.32)	5.64	(2.67)	7.82	(3.65)	4.36	(2.47)	5.36	(3.16)	3.09	(2.10)	6.73	(3.28)	6.91	(3.26)
	120	9.73	(4.45)	3.82	(2.29)	5.64	(2.81)	8.82	(3.89)	4.55	(2.15)	6.27	(3.17)	3.00	(1.65)	7.73	(3.50)	6.09	(3.20)
	150	5.73	(2.65)	4.73	(2.58)	6.00	(3.22)	7.82	(3.44)	5.09	(1.88)	6.91	(3.65)	3.27	(2.02)	6.91	(2.78)	6.36	(2.85)
Light-Headed	0	1.55	(0.65)	4.45	(3.06)	7.91	(4.37)	5.55	(3.0)	7.09	(4.23)	3.64	(2.45)	4.27	(2.16)	3.82	(2.44)	3.45	(1.96)
	30	6.36	(3.21)	4.27	(2.87)	9.09	(3.82)	7.64	(3.02)	15.00	(8.51)	4.18	(2.91)	17.00	(6.44)	8.55	(4.80)	11.27	(4.92)
	60	5.64	(3.94)	5.18	(2.94)	14.82	(6.17)	9.27	(3.02)	10.45	(5.49)	12.09	(6.53)	17.82	(5.17)	5.09	(2.47)	11.73	(5.34)
	90	5.64	(2.67)	5.00	(3.29)	14.18	(6.67)	7.18	(4.07)	8.18	(5.71)	12.09	(5.48)	12.64	(5.06)	5.27	(2.98)	17.45	(6.57)
	120	5.18	(2.83)	3.82	(2.32)	12.82	(5.43)	5.45	(2.92)	8.00	(5.72)	4.55	(2.77)	7.27	(3.59)	5.18	(3.11)	21.18	(6.66)
	150	5.27	(2.72)	3.36	(2.07)	12.00	(6.22)	4.55	(2.69)	8.82	(6.57)	9.73	(4.19)	5.36	(3.59)	4.73	(2.32)	15.36	(6.32)
Sleepy	0	24.55	(7.34)	15.45	(6.21)	24.18	(7.12)	27.82	(6.31)	25.18	(7.70)	22.82	(6.68)	28.55	(7.99)	36.64	(8.29)	26.27	(9.47)
	30	32.55	(8.45)	22.00	(7.24)	32.27	(7.87)	41.18	(8.95)	37.18	(11.35)	38.45	(5.77)	44.09	(10.31)	38.36	(7.77)	30.45	(9.82)
	60	32.91	(8.70)	22.82	(7.79)	43.36	(7.21)	46.55	(9.83)	27.45	(7.97)	40.82	(7.58)	45.64	(9.42)	43.27	(9.28)	36.73	(8.52)
	90	30.82	(9.30)	21.55	(6.90)	48.36	(8.59)	39.91	(9.64)	31.91	(10.10)	39.27	(7.92)	37.36	(8.73)	42.55	(9.52)	45.09	(6.18)
	120	34.18	(8.62)	30.09	(8.84)	44.45	(9.85)	37.91	(10.12)	32.64	(10.72)	40.09	(9.76)	24.00	(7.45)	34.82	(8.76)	44.00	(7.93)
	150	33.27	(8.98)	32.55	(9.23)	43.64	(10.29)	28.45	(9.90)	31.73	(9.92)	45.09	(6.75)	26.73	(8.94)	33.64	(8.38)	41.73	(7.24)
Restless	0	8.55	(3.83)	8.82	(6.04)	11.64	(4.85)	8.00	(3.50)	10.18	(5.49)	7.36	(3.31)	8.73	(4.59)	5.27	(2.36)	9.91	(4.67)
	30	7.27	(3.23)	5.91	(2.93)	10.36	(3.76)	12.00	(7.21)	8.00	(4.58)	7.00	(3.80)	7.45	(3.29)	10.82	(5.70)	10.82	(4.91)
	60	9.91	(4.23)	10.18	(4.68)	5.91	(2.76)	14.55	(7.21)	3.82	(2.0)	8.45	(4.37)	10.64	(5.23)	12.27	(5.98)	8.18	(3.61)
	90	8.27	(3.78)	7.64	(4.52)	10.36	(4.01)	9.91	(9.07)	3.82	(2.32)	7.45	(3.83)	7.82	(5.23)	8.09	(3.70)	8.45	(3.66)
	120	6.36	(2.96)	13.00	(6.09)	12.27	(5.65)	10.82	(6.55)	9.91	(4.90)	8.09	(3.98)	10.00	(5.08)	11.45	(4.11)	7.55	(3.36)
	150	8.00	(3.52)	13.64	(6.98)	11.09	(4.60)	5.64	(2.68)	5.09	(2.64)	12.45	(5.52)	10.55	(5.61)	10.64	(3.88)	12.00	(5.34)
Sick To Stomach	0	4.00	(2.66)	5.45	(3.02)	5.45	(2.53)	3.45	(2.08)	5.82	(2.69)	2.36	(1.54)	6.82	(3.36)	3.82	(2.63)	6.73	(3.02)
	30	7.55	(3.14)	3.91	(2.32)	10.36	(6.29)	4.55	(2.22)	3.55	(2.35)	9.64	(6.07)	4.18	(2.53)	5.55	(2.70)	6.73	(2.67)
	60	3.91	(2.64)	4.64	(2.62)	6.09	(2.59)	5.09	(2.76)	3.73	(2.01)	10.91	(6.87)	12.09	(9.11)	4.09	(2.70)	7.18	(3.85)
	90	5.55	(2.93)	2.64	(1.87)	6.82	(2.62)	4.55	(2.46)	4.45	(2.54)	11.64	(8.14)	7.27	(5.31)	12.27	(6.45)	8.00	(3.73)
	120	3.64	(2.29)	4.18	(2.72)	5.27	(2.35)	3.82	(2.33)	4.27	(2.34)	10.64	(7.36)	7.09	(4.48)	9.55	(4.89)	9.55	(3.35)
	150	4.36	(2.56)	4.45	(2.92)	7.00	(3.22)	3.36	(1.89)	4.45	(2.51)	7.73	(4.18)	4.00	(2.39)	7.18	(3.19)	7.18	(5.42)
Talkative	0	32.18	(7.89)	41.45	(7.68)	33.73	(9.25)	27.45	(5.03)	34.82	(9.26)	29.36	(8.43)	37.09	(6.98)	31.82	(6.04)	33.00	(8.79)
	30	26.82	(6.49)	39.09	(9.73)	32.18	(8.32)	23.18	(5.98)	23.27	(7.95)	26.82	(7.34)	22.55	(6.16)	27.09	(7.10)	26.91	(7.83)
	60	27.73	(7.11)	34.45	(8.01)	32.64	(6.92)	21.64	(4.82)	22.00	(7.80)	27.09	(6.80)	26.64	(6.32)	22.55	(5.13)	27.36	(6.07)
	90	26.36	(7.14)	35.82	(8.82)	33.00	(7.75)	24.73	(4.90)	27.36	(7.86)	27.64	(6.59)	25.36	(6.42)	26.45	(6.63)	27.91	(6.98)
	120	23.36	(7.10)	39.27	(9.71)	32.64	(7.14)	23.27	(6.28)	31.73	(8.33)	30.45	(7.24)	29.82	(6.84)	29.73	(7.96)	28.27	(6.59)
	150	28.82	(7.19)	37.73	(9.27)	35.82	(7.74)	24.55	(5.94)	29.00	(7.17)	24.09	(6.14)	31.64	(7.89)	29.82	(8.22)	30.36	(7.03)
Friendly	0	53.00	(6.71)	51.36	(8.18)	50.18	(8.05)	44.64	(5.80)	51.36	(8.08)	56.00	(7.21)	47.00	(6.74)	46.73	(7.79)	47.27	(9.39)
	30	42.64	(6.48)	47.55	(8.82)	51.55	(7.19)	37.27	(6.03)	37.64	(8.35)	38.27	(7.36)	39.91	(7.14)	44.36	(8.54)	41.45	(8.35)
	60	37.82	(7.94)	40.64	(7.67)	42.91	(7.27)	32.64	(6.03)	32.36	(8.02)	41.45	(7.40)	33.45	(6.90)	39.27	(9.13)	39.73	(6.85)
	90	31.55	(7.65)	42.82	(7.81)	39.36	(7.83)	32.82	(5.80)	46.55	(7.94)	36.36	(8.30)	33.45	(5.72)	39.09	(6.24)	35.36	(6.64)
	120	34.27	(8.0)	41.82	(7.95)	38.00	(8.07)	34.09	(7.18)	38.45	(8.84)	33.18	(7.80)	37.82	(6.51)	35.36	(8.07)	35.36	(6.81)
	150	41.55	(7.90)	41.09	(9.15)	39.91	(8.17)	39.45	(6.73)	35.73	(7.71)	33.91	(7.64)	38.82	(7.98)	38.00	(8.52)	36.73	(7.76)
Hungry	0	46.18	(9.44)	37.36	(10.01)	42.55	(8.78)	44.55	(8.40)	48.18	(10.68)	50.36	(10.13)	40.18	(10.08)	47.36	(8.89)	48.64	(9.53)
	30	7.45	(3.68)	4.00	(3.0)	10.18	(4.08)	5.82	(2.49)	8.91	(4.87)	9.91	(5.01)	12.18	(5.65)	9.09	(3.78)	6.27	(3.47)
	60	13.45	(5.13)	10.64	(4.16)	13.09	(5.31)	10.09	(2.49)	8.09	(4.60)	13.91	(5.28)	20.82	(8.15)	15.18	(5.38)	10.36	(4.55)
	90	18.73	(6.17)	14.00	(6.47)	18.36	(6.04)	12.91	(4.23)	12.82	(5.78)	15.36	(6.23)	23.27	(10.08)	17.55	(7.40)	14.73	(4.93)
	120	32.36	(7.92)	24.00	(8.28)	25.18	(8.35)	19.36	(7.44)	13.18	(5.44)	24.18	(8.68)	26.64	(10.60)	23.82	(8.21)	16.00	(6.12)
	150	39.27	(8.26)	28.82	(9.96)	32.55	(6.90)	19.55	(8.48)	25.27	(6.19)	31.55	(9.24)	34.36	(10.94)	33.18	(8.99)	27.27	(7.57)
Thirsty	0	33.73	(8.48)	18.55	(7.31)	22.64	(5.85)	25.18	(7.41)	29.09	(8.21)	23.09	(7.14)	21.36	(8.81)	33.00	(7.16)	19.73	(6.15)
	30	18.55	(6.37)	6.73	(2.72)	13.18	(5.69)	9.09	(3.03)	5.91	(2.88)	10.18	(4.77)	9.45	(4.74)	9.91	(3.80)	8.91	(4.11)
	60	13.73	(4.41)	10.00	(4.18)	10.82	(3.81)	8.91	(3.03)	5.36	(2.41)	9.36	(4.0)	10.82	(5.36)	10.45	(3.46)	10.73	(4.44)
	90	17.91	(5.52)	6.73	(3.54)	8.73	(3.24)	11.27	(3.12)	6.91	(2.71)	12.27	(4.94)	13.00	(6.70)	12.36	(4.29)	14.27	(4.59)
	120	21.00	(5.94)	9.82	(4.50)	14.00	(4.81)	10.09	(3.86)	10.27	(5.11)	13.09	(5.62)	11.27	(5.40)	15.55	(5.96)	15.55	(4.25)
	150	22.45	(6.95)	21.91	(7.24)	21.36	(6.53)	17.64	(6.11)	12.45	(5.53)	18.27	(7.24)	10.00	(4.29)	18.45	(5.28)	18.45	(4.39)

SELF-REPORT MEASURES		0 mg PROGESTERONE						100 mg PROGESTERONE						200 mg PROGESTERONE					
VAS	TIME	0.00		0.12		0.25		0.00		0.12		0.25		0.00		0.12		0.25	
Shaky	0	5.09	(2.89)	5.73	(3.26)	9.27	(4.66)	4.09	(2.10)	9.82	(4.37)	4.09	(2.16)	5.00	(2.62)	5.80	(2.62)	5.00	(2.93)
	30	5.00	(2.59)	6.91	(3.03)	9.82	(4.52)	4.55	(2.23)	5.00	(2.56)	4.18	(2.97)	7.20	(3.53)	4.60	(2.19)	4.64	(2.17)
	60	4.82	(2.96)	7.36	(3.77)	15.45	(6.58)	5.09	(2.99)	7.82	(5.69)	5.27	(2.43)	7.90	(2.90)	5.10	(2.16)	8.64	(3.63)
	90	5.18	(2.53)	3.91	(1.93)	11.27	(6.62)	5.36	(2.89)	3.91	(2.09)	5.73	(3.21)	2.70	(1.47)	6.40	(2.79)	9.55	(3.11)
	120	6.09	(2.78)	4.36	(2.80)	7.82	(4.94)	3.64	(2.08)	5.91	(3.22)	6.18	(2.61)	4.80	(2.43)	7.60	(3.17)	7.60	(4.23)
	150	5.64	(2.19)	4.91	(2.79)	7.73	(3.78)	4.36	(2.26)	6.73	(3.87)	6.55	(2.78)	3.30	(1.77)	8.90	(2.92)	8.90	(4.79)
Jittery	0	8.27	(3.54)	5.82	(3.10)	9.64	(4.99)	4.18	(2.12)	4.55	(3.19)	4.27	(1.80)	5.60	(3.13)	6.40	(3.15)	6.64	(3.09)
	30	6.91	(3.04)	7.00	(3.09)	8.36	(3.59)	6.36	(2.69)	4.73	(2.0)	4.55	(2.46)	5.80	(3.09)	6.30	(3.08)	5.18	(2.81)
	60	5.55	(2.38)	6.73	(3.63)	12.82	(5.69)	5.27	(2.93)	5.00	(2.56)	6.27	(3.0)	6.00	(2.76)	4.70	(2.05)	10.09	(4.59)
	90	5.73	(3.16)	5.45	(1.94)	11.36	(5.57)	4.82	(2.45)	3.36	(1.78)	6.82	(3.46)	3.60	(1.56)	7.50	(3.28)	11.45	(5.36)
	120	6.36	(2.96)	5.18	(2.39)	10.18	(5.61)	5.18	(2.52)	5.64	(3.08)	13.36	(6.12)	4.70	(1.94)	7.10	(3.02)	13.64	(4.31)
	150	5.00	(2.25)	6.36	(3.48)	10.09	(4.93)	4.09	(2.40)	5.64	(2.95)	8.18	(3.07)	5.00	(2.64)	5.50	(2.20)	11.27	(4.53)
Down	0	14.91	(7.79)	5.27	(3.15)	9.36	(5.81)	7.73	(2.88)	5.00	(2.78)	5.45	(3.02)	6.00	(2.55)	5.20	(2.26)	5.82	(2.45)
	30	8.00	(4.02)	3.45	(2.22)	3.73	(2.08)	6.45	(2.51)	4.36	(2.43)	5.00	(2.23)	4.50	(2.62)	3.60	(2.33)	4.00	(2.31)
	60	6.64	(3.21)	3.64	(2.45)	4.00	(2.13)	6.00	(2.51)	5.09	(2.23)	5.55	(1.76)	4.40	(2.39)	3.40	(1.86)	4.91	(2.66)
	90	5.00	(3.27)	2.73	(1.27)	2.82	(1.36)	6.73	(2.97)	6.55	(3.44)	4.09	(2.64)	3.40	(1.70)	4.20	(2.41)	5.91	(3.89)
	120	3.91	(2.33)	3.73	(2.68)	3.18	(1.91)	6.64	(3.0)	5.45	(3.04)	5.73	(2.55)	3.50	(1.81)	6.60	(3.30)	6.91	(2.93)
	150	4.73	(2.84)	3.45	(2.42)	5.64	(2.79)	10.82	(6.76)	3.09	(2.13)	5.55	(2.61)	3.40	(2.29)	5.90	(2.26)	2.91	(1.37)
Depressed	0	4.82	(2.75)	4.09	(3.37)	4.73	(2.32)	6.00	(3.44)	3.55	(2.25)	3.36	(1.96)	2.90	(2.27)	2.90	(1.61)	3.27	(1.62)
	30	8.09	(5.86)	2.00	(1.90)	3.55	(2.03)	5.27	(2.38)	4.00	(2.26)	3.36	(2.0)	3.20	(2.23)	3.90	(2.14)	2.36	(1.47)
	60	3.91	(2.55)	2.55	(2.17)	2.73	(1.33)	5.45	(2.89)	4.45	(2.37)	3.18	(1.52)	3.70	(2.27)	3.10	(1.53)	3.55	(2.05)
	90	4.36	(2.85)	2.36	(1.44)	4.45	(2.38)	5.73	(3.12)	3.09	(1.63)	3.36	(2.46)	3.90	(1.92)	3.90	(2.13)	5.18	(3.30)
	120	4.82	(3.12)	1.45	(1.05)	3.18	(1.89)	4.73	(2.97)	2.91	(2.08)	3.64	(1.76)	2.30	(1.53)	4.50	(2.50)	4.50	(2.09)
	150	4.00	(2.71)	2.55	(2.46)	3.09	(1.98)	4.91	(2.82)	3.18	(2.28)	6.45	(3.20)	2.30	(1.81)	4.20	(2.34)	4.20	(1.17)
High	0	2.55	(1.79)	4.55	(3.31)	3.18	(1.58)	3.09	(1.69)	2.73	(1.70)	2.82	(1.99)	3.20	(2.03)	3.30	(1.80)	3.00	(1.69)
	30	3.64	(1.88)	2.82	(1.83)	3.55	(1.95)	2.36	(1.78)	4.73	(2.29)	5.09	(3.01)	4.90	(2.51)	6.40	(2.50)	8.82	(5.14)
	60	2.82	(2.16)	3.00	(2.28)	4.73	(3.25)	7.27	(3.48)	4.64	(2.32)	3.00	(1.67)	7.30	(3.96)	5.80	(2.81)	9.64	(3.70)
	90	4.36	(2.90)	2.27	(1.65)	8.73	(5.42)	5.73	(3.23)	3.64	(1.97)	3.09	(2.16)	2.90	(2.02)	5.00	(2.58)	7.55	(3.33)
	120	2.64	(1.78)	2.82	(1.77)	7.09	(4.12)	3.27	(2.18)	3.82	(2.22)	3.00	(2.43)	2.60	(1.42)	8.60	(4.54)	8.91	(4.33)
	150	3.45	(2.51)	3.27	(2.09)	7.36	(5.44)	2.64	(1.88)	4.36	(2.36)	4.27	(2.91)	4.80	(2.80)	4.20	(2.18)	7.82	(3.61)
Euphoric	0	3.91	(2.01)	5.09	(3.22)	4.91	(2.46)	3.45	(1.96)	3.18	(1.73)	2.45	(1.47)	2.60	(1.59)	4.20	(2.15)	4.91	(2.39)
	30	8.64	(3.66)	1.82	(1.26)	4.55	(2.64)	3.36	(1.57)	4.09	(2.46)	7.45	(3.36)	4.60	(2.38)	4.50	(2.34)	6.73	(3.79)
	60	4.73	(2.51)	2.00	(1.32)	5.00	(2.21)	6.82	(1.57)	5.55	(2.49)	3.73	(1.97)	7.70	(4.19)	5.80	(2.99)	9.64	(3.89)
	90	3.27	(1.96)	3.55	(2.06)	5.73	(3.18)	6.73	(3.83)	4.00	(2.50)	6.64	(3.22)	6.40	(1.34)	4.30	(1.93)	8.55	(3.34)
	120	2.64	(1.41)	4.09	(2.63)	6.82	(3.86)	5.18	(2.68)	3.55	(2.22)	5.45	(2.51)	2.80	(1.55)	6.50	(3.35)	7.00	(3.79)
	150	3.09	(2.02)	3.82	(2.0)	6.45	(3.89)	3.64	(2.24)	3.09	(1.54)	3.55	(2.19)	3.30	(2.01)	4.80	(2.29)	8.36	(3.16)
Active	0	21.55	(6.70)	42.91	(7.33)	30.45	(9.09)	23.45	(5.68)	35.55	(8.56)	35.09	(9.21)	34.20	(8.11)	33.80	(5.97)	34.00	(9.40)
	30	20.91	(5.54)	31.00	(7.71)	26.73	(6.17)	12.64	(3.77)	20.27	(6.61)	17.55	(5.95)	22.00	(6.58)	24.20	(6.37)	23.55	(7.44)
	60	15.64	(5.28)	27.36	(8.93)	19.09	(5.28)	10.73	(2.52)	19.00	(5.71)	16.64	(6.35)	22.40	(5.93)	16.60	(5.89)	25.00	(7.56)
	90	17.18	(5.58)	30.36	(7.78)	24.45	(5.20)	12.91	(2.91)	21.82	(5.31)	18.18	(6.35)	18.80	(5.11)	19.50	(6.10)	20.36	(7.26)
	120	19.91	(7.04)	29.00	(7.88)	27.00	(6.86)	12.82	(2.85)	25.64	(5.77)	20.00	(6.27)	22.90	(5.43)	18.50	(5.79)	22.45	(6.62)
	150	20.09	(7.34)	29.64	(8.11)	28.64	(5.74)	21.73	(4.95)	24.82	(6.39)	20.18	(5.38)	23.30	(4.41)	18.90	(6.30)	21.09	(6.98)
Alert	0	34.91	(6.85)	46.27	(7.72)	40.82	(9.34)	31.27	(7.77)	39.27	(9.68)	42.64	(9.07)	35.70	(8.99)	36.40	(7.94)	40.91	(9.01)
	30	26.91	(6.20)	37.36	(8.13)	36.91	(7.80)	20.09	(6.36)	28.27	(9.26)	25.27	(6.27)	27.50	(7.67)	26.60	(6.46)	21.64	(6.25)
	60	27.18	(7.04)	33.09	(9.53)	28.91	(6.35)	17.09	(6.36)	25.73	(7.41)	20.36	(7.71)	27.20	(7.10)	19.40	(4.48)	23.45	(6.18)
	90	23.82	(7.35)	36.18	(9.51)	26.64	(6.14)	28.82	(4.48)	25.82	(6.11)	19.82	(5.67)	23.50	(8.17)	22.10	(5.29)	21.45	(6.13)
	120	33.82	(8.68)	34.27	(8.87)	32.64	(7.62)	20.18	(3.87)	28.91	(6.51)	22.36	(6.16)	35.20	(8.03)	25.70	(5.50)	27.00	(6.51)
	150	28.82	(8.27)	32.73	(8.55)	33.09	(6.16)	31.73	(5.49)	30.45	(7.10)	22.64	(6.08)	31.10	(7.79)	30.80	(7.12)	26.45	(6.15)
Energetic	0	28.09	(6.34)	39.36	(7.79)	31.27	(8.10)	20.27	(5.81)	37.55	(9.37)	37.09	(8.89)	31.40	(8.71)	29.10	(6.60)	34.18	(9.60)
	30	23.27	(6.35)	31.09	(9.61)	23.36	(4.92)	11.18	(3.29)	23.45	(7.76)	17.00	(5.98)	17.60	(5.25)	23.80	(6.98)	21.91	(7.59)
	60	21.00	(6.93)	27.55	(8.22)	18.27	(5.19)	9.27	(3.70)	16.82	(6.02)	16.27	(6.78)	21.60	(6.48)	17.90	(6.45)	23.55	(8.27)
	90	20.82	(6.89)	32.36	(8.64)	17.73	(5.94)	12.73	(3.63)	22.27	(6.52)	16.45	(6.41)	13.30	(5.02)	17.50	(5.76)	16.55	(6.60)
	120	22.09	(7.05)	29.09	(8.45)	24.55	(7.06)	12.55	(2.91)	21.91	(5.16)	16.73	(6.45)	22.30	(5.87)	19.30	(6.06)	19.30	(6.92)
	150	22.45	(7.70)	28.91	(7.98)	22.36	(6.39)	18.36	(4.74)	23.18	(6.65)	17.36	(4.73)	18.60	(4.28)	20.90	(5.80)	20.90	(6.60)
Rush	0	0.27	(0.15)	0.55	(0.57)	1.73	(1.41)	1.64	(1.42)	0.36	(0.29)	0.91	(0.67)	2.40	(2.40)	1.90	(1.68)	1.18	(0.85)
	30	4.64	(2.81)	2.09	(1.24)	7.73	(3.80)	6.18	(3.17)	16.27	(8.61)	11.73	(5.22)	18.30	(6.55)	7.40	(5.57)	8.18	(5.16)
	60	3.45	(2.45)	2.73	(1.67)	8.00	(5.19)	10.45	(6.06)	13.55	(6.92)	5.91	(4.61)	14.80	(6.23)	4.00	(2.20)	14.82	(5.97)
	90	2.27	(1.89)	2.73	(1.77)	7.45	(4.71)	3.73	(2.68)	12.73	(7.23)	2.36	(1.61)	7.00	(2.99)	5.10	(3.22)	17.00	(4.85)
	120	3.36	(2.73)	3.73	(1.73)	12.27	(6.43)	2.64	(1.72)	12.64	(7.78)	14.45	(6.71)	8.40	(7.12)	4.10	(2.13)	18.18	(6.56)
	150	2.55	(2.16)	2.82	(1.85)	7.36	(3.75)	2.00	(1.59)	11.73	(6.88)	14.73	(7.43)	6.70	(5.62)	8.20	(5.70)	21.55	(7.05)
Performance Impaired	0	0.45	(0.33)	0.36	(0.21)	0.82	(0.37)	1.18	(0.94)	0.18	(0.13)	0.27	(0.20)	1.50	(1.39)	1.90	(1.46)	0.73	(0.53)
	30	4.09	(2.36)	2.82	(1.38)	7.91	(3.15)	6.64	(3.13)	16.55	(8.59)	10.18	(5.38)	25.20	(6.93)	14.50	(6.39)	13.73	(5.91)
	60	6.82	(4.54)	3.45	(1.88)	21.91	(8.17)	19.00	(3.13)	18.45	(7.52)	20.45	(8.71)	23.50	(7.07)	19.70	(8.49)	24.00	(7.02)
	90	8.36	(5.74)	4.45	(2.84)	19.73	(8.47)	10.82	(7.02)	16.09	(10.30)	16.27	(7.38)	16.70	(6.89)	28.70	(10.37)	40.09	(9.06)
	120	7.45	(6.29)	3.73	(2.05)	25.64	(8.98)	10.73	(5.27)	18.82	(9.65)	18.82	(9.03)	9.60	(5.74)	23.70	(9.88)	41.73	(8.85)
	150	9.73	(6.17)	2.91	(1.70)	22.91	(9.80)	8.18	(3.42)	18.55	(8.91)	17.09	(7.10)	6.40	(4.70)	16.50	(6.79)	40.64	###
Performance Improved	0	0.27	(0.20)	0.64	(0.38)	1.64	(1.13)	1.09	(0.94)	0.45	(0.26)	0.73	(0.32)	1.30	(1.09)	1.50	(1.50)	1.55	(1.02)
	30	1.36	(0.80)	2.18	(1.69)	2.18	(1.14)	1.91	(1.80)	8.18	(5.25)	2.73	(2.18)	2.80	(2.11)	3.00	(2.08)	5.55	(3.40)
	60	6.18	(3.55)	3.18	(1.74)	5.45	(3.09)	3.00	(2.04)	5.36	(3.02)	4.09	(2.48)	3.50	(2.17)	2.00	(1.29)	7.09	(5.30)
	90	2.18	(1.31)	2.09	(1.69)	6.45	(4.38)	3.18	(1.95)	4.18	(2.12)	3.00	(1.69)	2.30	(1.98)	6.30	(4.65)	8.64	(4.56)
	120	2.18	(1.68)	2.18	(1.33)	7.36	(4.52)	4.00	(2.26)	7.55	(7.29)	1.82	(1.30)	1.40	(0.90)	5.70	(3.43)	5.70	(6.95)
	150	2.55	(1.50)	3.00	(1.70)	5.09	(3.75)	3.00	(2.20)	5.18	(4.10)	4.09	(3.38)	0.80	(0.61)	5.10	(3.12)	5.10	(3.42)
Drug Effect	0	0.09	(0.10)	0.36	(0.29)	1.27	(1.04)	1.09	(0.94)	0.27	(0.15)	0.09	(0.10)	1.50	(1.28)	0.90	(0.80)	0.82	(0.58)
	30	9.36	(4.79)	3.55	(1.53)	11.27	(3.67)	21.09	(7.69)	24.64	(8.47)	20.36	(6.28)	31.60	(8.08)	29.00	(8.68)	23.64	(8.68)
	60	8.82	(3.86)	5.64	(2.81)	23.00	(9.11)	24.55	(7.69)	30.82	(8.94)	28.18	(8.94)	29.20	(6.26)	24.30	(8.48)	30.82	(8.66)
	90	9.27	(5.01)	6.91	(2.92)	27.36	(9.05)	15.45	(7.93)	27.00	(9.61)	23.64	(9.94)	19.10	(7.50)	33.20	(9.72)	46.45	(8.51)
	120	9.00	(5.25)	7.18	(2.80)	28.55	(9.73)	17.09	(8.52)	23.64	(10.56)	28.55	(9.84)	14.20	(7.30)	24.40	(9.0)	32.00	(8.99)
	150	9.36	(5.05)	7.18	(3.23)	27.91	(9.79)	14.73	(7.49)	21.00	(9.86)	28.82	(9.61)	4.30	(3.46)	18.50	(6.56)	46.45	(9.48)
Good Drug Effect	0	0.45	(0.17)	1.09	(0.68)	0.73	(0.40)	1.09	(1.14)	0.18	(0.13)	0.45	(0.38)	1.30	(1.19)	1.80	(1.58)	0.64	(0.38)
	30	8.36	(3.76)	5.91	(4.04)	9.00	(4.85)	4.27	(2.24)	16.00	(5.78)	14.36	(5.86)	16.40	(5.88)	6.30	(2.46)	5.36	(1.88)
	60	6.45	(3.10)	6.82	(3.54)	9.09	(4.54)	12.36	(4.55)	13.55	(4.93)	10.64	(4.70)	12.70	(4.26)	3.50	(1.56)	10.09	(3.38)
	90	5.36	(3.04)	2.36	(1.58)	8.55	(5.20)	6.36	(2.74)	11.64	(6.07)	7.18	(4.27)	9.50	(3.86)	11.70	(4.86)	19.91	(5.45)
	120	5.18	(3.50)	4.27	(1.99)	8.55	(5.14)	2.82	(1.54)	9.36	(5.56)	9.45	(4.44)	5.80	(2.46)	8.10	(4.95)	8.10	(5.63)
	150	8.45	(5.20)	4.00	(2.14)	8.73	(4.63)	4.09	(2.02)	6.82	(4.55)	6.64	(4.20)	1.50	(1.19)	6.30	(4.54)	6.30	(5.30)
Bad Drug Effect	0	0.45	(0.30)	0.27	(0.15)	0.64	(0.50)	1.45	(1.33)	0.27	(0.15)	0.09	(0.10)	1.20	(1.09)	1.40	(1.09)	0.73	(0.57)
	30	7.73	(4.95)	5.73	(3.66)	11.36	(5.06)	11.18	(4.51)	13.18	(5.63)	13.91	(6.98)	11.40	(5.20)	8.10	(3.04)	8.36	(3.40)
	60	6.91	(4.53)	5.73	(2.86)	9.82	(5.44)	11.36	(5.21)	17.73	(8.31)	8.45	(4.97)	16.00	(7.34)	14.70	(6.80)	10.64	(4.18)
	90	7.09	(5.70)	4.27	(2.20)	10.27	(5.14)	10.27	(4.39)	17.91	(7.82)	5.91	(4.64)	18.40	(10.46)	24.50	(8.05)	25.91	(6.52)
	120	5.73	(4.51)	4.45	(2.11)	15.82	(5.30)	8.00	(4.13)	12.18	(6.89)	9.64	(4.86)	8.10	(5.29)	19.30	(8.72)	21.64	(5.46)
	150	9.73	(5.71)	6.91	(2.71)	13.91	(7.57)	7.45	(3.85)	10.55	(6.04)	9.09	(4.63)	1.10	(0.89)	15.70	(5.74)	26.27	(8.09)
Like Drug Effect	0	0.36	(0.16)	9.00	(6.11)	1.27	(0.66)	1.55	(1.31)	5.91	(4.56)	0.64	(0.50)	0.90	(0.80)	5.70	(4.72)	5.64	(4.51)
	30	12.00	(5.38)	11.18	(4.83)	10.09	(5.32)	7.73	(3.42)	17.55	(5.76)	16.82	(5.85)	14.50	(5.16)	11.30	(4.61)	14.55	(5.55)
	60	20.09	(6.96)	10.55	(5.75)	8.36	(4.31)	11.18	(4.16)	16.55	(6.43)	13.82	(5.75)	23.00	(5.78)	8.20	(3.08)	17.55	(4.58)
	90	15.45	(7.14)	11.64	(4.49)	13.82	(5.58)	14.18	(4.46)	14.45	(5.80)	15.73	(6.29)	14.30	(6.18)	13.40	(4.87)	24.55	(6.80)
	120	15.55	(7.15)	13.09	(5.27)	14.18	(6.30)	9.36	(4.77)	15.36	(7.43)	12.09	(4.82)	10.70	(5.49)	16.10	(6.32)	18.27	(6.18)
	150	18.18	(8.04)	11.82	(5.53)	16.09	(5.48)	11.00	(4.69)	21.55	(8.73)	14.45	(6.13)	15.50	(6.01)	15.40	(7.15)	24.36	(6.31)
Willing to Take Again	0	8.27	(6.33)	21.82	(10.0)	31.91	(11.29)	16.27	(9.07)	28.45	(9.60)	23.82	(10.84)	31.00	(10.69)	23.80	(10.08)	28.91	(9.86)
	30	34.45	(8.47)	36.00	(8.77)	43.82	(10.03)	39.27	(11.14)	41.00	(7.97)	39.18	(8.38)	40.00	(8.49)	33.40	(10.13)	38.73	(9.11)
	60	36.00	(8.46)	32.27	(9.67)	40.36	(10.42)	24.64	(11.14)	39.18	(8.28)	34.36	(7.61)	36.10	(8.31)	37.70	(9.50)	42.00	(8.97)
	90	30.27	(8.84)	39.36	(8.06)	39.55	(9.99)	29.91	(8.97)	36.45	(9.39)	29.55	(8.81)	37.30	(9.32)	41.30	(9.45)	38.55	(9.94)
	120	29.00	(8.79)	40.73	(8.76)	40.09	(10.57)	33.09	(9.65)	37.82	(9.61)	37.27	(7.93)	38.00	(8.71)	31.80	(8.97)	46.36	(8.98)
	150	37.27	(9.22)	36.82	(9.09)	45.09	(9.52)	34.09	(10.16)	38.82	(9.16)	39.64	(7.76)	37.80	(8.63)	35.60	(10.54)	47.82	(8.04)
Pay For Drug	0	0.36	(0.16)	2.73	(1.86)	1.36	(0.80)	4.82	(3.91)	5.00	(4.63)	1.82	(1.22)	4.20	(2.15)	0.50	(0.40)	3.45	(1.94)
	30	5.64	(4.43)	5.73	(2.53)	4.36	(2.45)	7.09	(4.07)	5.00	(2.42)	9.64	(5.08)	4.40	(2.63)	2.40	(1.66)	9.36	(3.98)
	60	7.91	(5.13)	4.73	(1.84)	4.64	(3.85)	5.64	(4.45)	4.55	(2.83)	5.18	(2.43)	5.00	(3.43)	3.80	(1.87)	9.27	(3.47)
	90	8.09	(5.51)	6.36	(2.80)	4.82	(3.39)	4.82	(2.42)	7.09	(4.18)	6.73	(4.53)	5.20	(2.96)	4.30	(2.30)	15.18	(6.38)
	120	14.91	(8.49)	6.45	(2.77)	4.27	(3.01)	5.45	(2.36)	7.00	(4.53)	7.45	(4.74)	2.00	(1.53)	4.80	(2.20)	4.80	(6.82)
	150	7.64	(5.06)	5.18	(2.37)	6.64	(3.74)	7.36	(3.76)	7.18	(3.38)	11.64	(5.20)	3.20	(1.67)	3.30	(1.31)	3.30	(5.24)
Irregular/Racing HR	0	3.09	(1.66)	4.36	(3.31)	3.09	(1.69)	2.64	(1.57)	4.45	(4.26)	3.36	(2.18)	2.90	(1.81)	3.30	(1.77)	3.18	(1.54)
	30	3.45	(2.43)	1.64	(1.23)	2.00	(1.17)	2.82	(1.80)	4.73	(3.14)	4.18	(2.43)	5.40	(4.16)	3.70	(2.06)	5.45	(2.69)
	60	6.09	(3.09)	3.45	(2.38)	5.18	(3.60)	4.55	(2.88)	3.55	(2.29)	2.09	(1.04)	4.80	(3.21)	3.00	(1.63)	4.45	(2.66)
	90	3.55	(2.36)	3.91	(2.81)	9.09	(5.93)	3.36	(2.36)	5.09	(3.56)	2.73	(1.77)	4.00	(2.84)	1.80	(0.92)	5.91	(3.15)
	120	5.18	(2.81)	2.45	(1.58)	8.64	(5.77)	2.73	(1.91)	4.45	(3.17)	3.18	(1.74)	3.20	(2.87)	5.00	(2.37)	5.00	(2.74)
	150	3.18	(2.05)	3.18	(1.80)	6.18	(4.24)	3.00	(2.06)	6.27	(4.45)	3.00	(1.75)	4.20	(2.70)	4.90	(2.36)	4.90	(2.71)

		0 mg PROGESTERONE						100 mg PROGESTERONE						200 mg PROGESTERONE					
SELF-REPORT MEASURES																			
VAS	**TIME**	**0.00**		**0.12**		**0.25**		**0.00**		**0.12**		**0.25**		**0.00**		**0.12**		**0.25**	
ARS																			
Sedative	0	7.73	(1.65)	5.73	(1.90)	8.09	(2.17)	6.18	(1.75)	7.91	(2.69)	7.00	(1.82)	7.00	(2.09)	6.73	(1.69)	6.55	(1.76)
	30	8.55	(1.73)	7.18	(2.14)	7.64	(1.51)	8.82	(1.90)	11.55	(3.48)	10.45	(1.81)	12.18	(2.56)	13.09	(2.48)	11.18	(2.78)
	60	8.91	(1.63)	8.45	(2.34)	10.27	(2.32)	10.64	(1.90)	12.27	(3.13)	13.73	(2.92)	13.18	(2.38)	14.36	(2.98)	12.00	(2.60)
	90	8.09	(1.26)	8.91	(2.25)	10.82	(2.32)	10.00	(2.72)	10.82	(3.48)	13.00	(2.93)	10.91	(2.09)	12.91	(2.66)	13.64	(1.92)
	120	8.45	(1.14)	9.27	(2.53)	10.27	(2.87)	8.64	(1.85)	10.82	(3.96)	12.91	(3.41)	7.64	(1.77)	10.45	(2.33)	15.55	(2.87)
	150	7.55	(1.50)	8.55	(2.62)	11.73	(3.12)	7.55	(2.25)	10.18	(3.81)	12.82	(2.97)	6.45	(1.88)	9.27	(2.05)	13.45	(2.36)
ARCI																			
PCAG SCALE	0	4.27	(0.87)	3.73	(0.72)	3.91	(0.54)	4.64	(0.72)	3.64	(0.85)	3.91	(0.92)	4.55	(0.92)	4.09	(0.71)	4.36	(0.96)
	30	5.27	(1.08)	4.91	(1.14)	4.73	(1.04)	6.73	(0.93)	6.09	(1.35)	6.55	(1.26)	8.64	(1.21)	7.64	(0.95)	6.82	(1.31)
	60	6.27	(0.92)	5.73	(1.25)	6.82	(1.10)	7.27	(0.93)	7.45	(1.31)	7.64	(1.44)	8.36	(1.20)	8.36	(1.11)	7.45	(1.34)
	90	6.09	(1.09)	5.45	(1.19)	7.55	(1.37)	6.64	(0.95)	7.09	(1.24)	7.36	(1.55)	7.27	(1.23)	8.00	(1.25)	9.73	(1.11)
	120	6.27	(1.12)	6.00	(1.25)	7.36	(1.46)	6.45	(1.11)	6.09	(1.35)	7.91	(1.51)	6.00	(1.21)	7.73	(1.23)	10.09	(1.36)
	150	5.09	(0.84)	6.73	(1.53)	7.73	(1.29)	5.36	(0.71)	5.91	(1.31)	8.36	(1.37)	4.55	(0.82)	7.18	(1.38)	10.27	(1.18)
BG SCALE	0	5.45	(0.54)	6.18	(0.90)	4.55	(0.67)	5.09	(0.57)	6.27	(0.75)	5.27	(0.47)	5.27	(0.63)	5.82	(0.86)	4.64	(0.62)
	30	5.27	(0.78)	5.27	(0.95)	4.45	(0.73)	4.18	(0.69)	3.91	(0.89)	4.18	(0.65)	3.55	(0.48)	3.91	(0.68)	3.91	(0.46)
	60	4.64	(0.80)	4.64	(1.11)	3.82	(0.75)	3.73	(0.78)	3.64	(0.89)	3.73	(0.74)	3.18	(0.79)	3.36	(0.57)	3.45	(0.67)
	90	4.09	(0.83)	5.00	(1.01)	3.45	(0.89)	4.09	(0.79)	4.09	(0.78)	3.64	(0.75)	3.09	(0.62)	3.45	(0.61)	3.09	(0.52)
	120	4.36	(0.84)	4.45	(1.19)	3.73	(0.96)	3.82	(0.85)	4.27	(0.81)	3.82	(0.85)	3.73	(0.62)	4.18	(0.54)	4.18	(0.86)
	150	4.91	(0.61)	4.55	(1.16)	3.45	(0.79)	4.64	(0.78)	4.45	(0.79)	3.64	(0.74)	4.55	(0.52)	3.73	(0.69)	3.73	(0.58)
LSD SCALE	0	2.82	(0.34)	2.73	(0.25)	3.09	(0.22)	2.64	(0.32)	3.09	(0.33)	2.82	(0.37)	2.82	(0.24)	3.00	(0.28)	3.36	(0.64)
	30	2.82	(0.31)	3.09	(0.33)	3.18	(0.40)	3.36	(0.41)	3.18	(0.24)	3.27	(0.43)	3.36	(0.35)	3.45	(0.54)	3.55	(0.41)
	60	2.55	(0.30)	3.55	(0.52)	3.64	(0.29)	3.18	(0.47)	3.55	(0.30)	3.36	(0.64)	3.55	(0.55)	3.36	(0.50)	3.09	(0.39)
	90	2.91	(0.39)	3.45	(0.52)	3.45	(0.41)	2.82	(0.44)	3.36	(0.38)	3.36	(0.45)	3.36	(0.47)	3.36	(0.57)	3.55	(0.48)
	120	2.73	(0.32)	3.91	(0.57)	3.18	(0.42)	2.73	(0.35)	3.36	(0.38)	3.55	(0.77)	2.73	(0.45)	3.82	(0.69)	3.82	(0.72)
	150	3.00	(0.32)	3.36	(0.47)	3.55	(0.41)	2.73	(0.40)	3.45	(0.52)	3.27	(0.78)	2.82	(0.31)	3.55	(0.46)	3.36	(0.65)
MBG SCALE	0	3.00	(0.91)	3.45	(1.29)	1.36	(0.43)	3.18	(1.12)	3.91	(0.95)	2.27	(0.91)	1.55	(0.30)	2.55	(0.86)	1.36	(0.38)
	30	2.55	(0.80)	2.45	(0.97)	2.09	(0.74)	1.09	(0.43)	2.18	(0.58)	1.64	(0.82)	1.36	(0.43)	0.91	(0.43)	1.09	(0.48)
	60	2.09	(0.99)	1.45	(0.54)	2.00	(1.12)	1.09	(0.43)	1.73	(0.40)	1.45	(0.59)	1.82	(0.51)	1.18	(0.54)	0.82	(0.44)
	90	1.82	(0.89)	2.36	(0.98)	1.45	(0.85)	1.27	(0.57)	1.64	(0.50)	1.82	(0.65)	1.09	(0.39)	1.09	(0.50)	1.09	(0.62)
	120	2.36	(1.27)	2.09	(0.75)	1.64	(0.77)	1.45	(0.77)	1.82	(0.44)	1.64	(0.59)	1.09	(0.30)	0.91	(0.43)	2.64	(1.53)
	150	2.09	(0.78)	1.64	(0.65)	2.18	(1.21)	1.55	(0.61)	2.00	(0.51)	1.45	(0.54)	1.27	(0.35)	1.00	(0.45)	0.82	(0.47)
A SCALE	0	2.45	(0.54)	3.18	(0.79)	2.27	(0.51)	2.45	(0.52)	3.00	(0.63)	2.18	(0.37)	2.18	(0.53)	2.45	(0.52)	1.91	(0.36)
	30	2.36	(0.59)	3.00	(0.72)	1.82	(0.49)	1.64	(0.45)	2.09	(0.61)	2.36	(0.59)	1.91	(0.46)	1.73	(0.40)	1.91	(0.43)
	60	1.91	(0.56)	2.45	(0.67)	2.36	(0.60)	2.18	(0.58)	2.00	(0.63)	2.45	(0.61)	2.27	(0.57)	1.55	(0.43)	1.91	(0.54)
	90	1.91	(0.52)	2.82	(0.68)	1.82	(0.49)	1.91	(0.52)	2.45	(0.64)	2.36	(0.57)	1.73	(0.40)	1.55	(0.22)	1.82	(0.51)
	120	1.91	(0.54)	2.64	(0.79)	2.09	(0.57)	1.82	(0.54)	2.18	(0.54)	2.09	(0.43)	2.00	(0.57)	1.91	(0.59)	1.91	(0.98)
	150	2.27	(0.51)	2.64	(0.77)	2.36	(0.52)	2.36	(0.65)	2.36	(0.65)	2.27	(0.49)	2.00	(0.42)	1.91	(0.52)	1.91	(0.40)
PERFORMANCE MEASURES																			
DSST																			
Total Trials	0	79.55	(3.24)	84.82	(3.24)	82.82	(2.28)	81.00	(3.30)	83.36	(2.46)	83.18	(3.15)	82.55	(2.16)	81.18	(3.12)	82.82	(2.88)
	30	80.55	(3.07)	84.09	(2.65)	82.64	(2.48)	80.09	(3.15)	82.91	(2.67)	82.55	(3.54)	80.45	(2.08)	77.36	(3.14)	79.82	(3.31)
	60	81.36	(2.78)	84.64	(2.71)	81.18	(2.82)	80.82	(3.15)	81.64	(2.21)	81.27	(3.41)	80.73	(2.93)	77.27	(3.69)	80.82	(3.40)
	90	82.36	(2.93)	84.82	(2.43)	79.36	(3.52)	82.73	(3.30)	80.73	(2.34)	79.27	(3.66)	83.27	(2.21)	78.73	(3.58)	75.55	(5.40)
	120	81.82	(2.89)	83.27	(2.75)	76.91	(3.40)	83.09	(3.29)	82.27	(2.65)	77.45	(4.92)	83.18	(2.24)	81.09	(3.38)	76.36	(5.09)
	150	82.82	(2.75)	83.18	(2.94)	78.27	(2.56)	83.64	(3.07)	82.18	(2.95)	77.36	(4.33)	83.45	(2.02)	80.55	(3.45)	75.73	(3.48)
Correct	0	74.27	(2.93)	80.82	(3.08)	78.64	(2.26)	75.68	(2.81)	77.82	(2.27)	77.00	(2.86)	78.55	(2.30)	75.64	(3.22)	77.64	(2.28)
	30	75.82	(2.76)	78.18	(2.70)	77.00	(2.56)	75.91	(2.95)	78.09	(2.36)	77.36	(2.80)	76.00	(2.32)	72.64	(3.06)	75.36	(3.21)
	60	75.82	(2.09)	80.09	(2.46)	76.55	(2.38)	74.27	(2.24)	77.45	(1.84)	76.00	(3.12)	77.09	(3.19)	70.09	(3.57)	76.36	(3.09)
	90	76.64	(2.70)	79.73	(2.10)	75.00	(3.36)	75.82	(2.81)	75.00	(2.45)	73.27	(3.37)	79.00	(1.98)	73.36	(3.45)	69.55	(5.54)
	120	76.45	(2.57)	76.91	(2.29)	70.45	(2.95)	76.91	(3.29)	77.45	(2.27)	70.18	(4.48)	78.09	(2.50)	74.73	(2.90)	74.73	(5.29)
	150	77.82	(2.23)	76.73	(2.56)	73.00	(1.97)	77.73	(2.57)	76.18	(3.07)	69.64	(4.41)	79.09	(1.91)	74.00	(2.84)	74.00	(3.93)
Errors	0	5.27	(0.91)	4.00	(0.71)	4.18	(0.96)	5.82	(1.10)	5.55	(1.10)	6.18	(1.22)	4.00	(0.86)	5.55	(0.97)	5.18	(1.17)
	30	4.73	(1.03)	5.91	(1.0)	5.64	(0.95)	4.18	(0.86)	4.82	(1.10)	5.18	(1.08)	4.45	(0.75)	4.73	(1.0)	4.45	(1.22)
	60	5.55	(1.19)	4.55	(0.84)	4.64	(0.83)	6.55	(1.37)	4.18	(0.61)	5.27	(0.81)	3.64	(0.93)	7.18	(1.33)	4.45	(0.82)
	90	5.73	(0.91)	5.09	(1.04)	4.36	(0.67)	6.91	(1.48)	5.73	(0.80)	6.00	(1.14)	4.27	(0.93)	5.36	(0.94)	6.00	(0.96)
	120	5.36	(0.72)	6.36	(1.34)	6.45	(1.04)	6.18	(1.11)	4.82	(0.97)	7.27	(1.10)	5.09	(0.94)	6.36	(0.79)	6.64	(2.29)
	150	5.00	(0.98)	6.45	(0.85)	5.27	(1.01)	5.91	(0.92)	6.00	(0.86)	7.73	(0.91)	4.36	(0.83)	6.55	(1.15)	6.55	(1.90)
Proportion Correct	0	0.93	(0.01)	0.95	(0.01)	0.95	(0.01)	0.93	(0.01)	0.93	(0.01)	0.93	(0.01)	0.95	(0.01)	0.93	(0.01)	0.94	(0.01)
	30	0.94	(0.01)	0.93	(0.01)	0.93	(0.01)	0.95	(0.01)	0.94	(0.01)	0.94	(0.01)	0.94	(0.01)	0.94	(0.01)	0.94	(0.02)
	60	0.93	(0.01)	0.95	(0.01)	0.94	(0.01)	0.92	(0.01)	0.95	(0.01)	0.94	(0.01)	0.95	(0.01)	0.91	(0.02)	0.95	(0.01)
	90	0.93	(0.01)	0.94	(0.01)	0.95	(0.01)	0.92	(0.01)	0.93	(0.01)	0.92	(0.01)	0.95	(0.01)	0.93	(0.01)	0.92	(0.01)
	120	0.94	(0.01)	0.93	(0.02)	0.92	(0.01)	0.93	(0.01)	0.94	(0.01)	0.91	(0.01)	0.94	(0.01)	0.92	(0.01)	0.90	(0.04)
	150	0.94	(0.01)	0.92	(0.01)	0.93	(0.01)	0.93	(0.01)	0.93	(0.01)	0.90	(0.02)	0.95	(0.01)	0.92	(0.01)	0.91	(0.03)
BART																			
Earning	0	6.20	(0.50)	5.94	(0.34)	6.31	(0.40)	5.62	(0.53)	5.57	(0.29)	6.30	(0.63)	6.60	(0.22)	5.90	(0.42)	5.69	(0.31)
	30	5.42	(0.45)	5.93	(0.41)	5.32	(0.42)	5.27	(0.32)	5.78	(0.41)	6.45	(0.42)	6.11	(0.48)	4.90	(0.35)	5.56	(0.29)
	60	5.70	(0.38)	5.91	(0.51)	6.16	(0.29)	5.38	(0.41)	6.29	(0.42)	6.09	(0.43)	5.67	(0.51)	5.04	(0.38)	6.05	(0.26)
	90	6.39	(0.57)	6.25	(0.40)	5.71	(0.45)	5.84	(0.53)	6.12	(0.28)	6.06	(0.51)	6.39	(0.15)	5.05	(0.25)	5.12	(0.36)
	120	6.08	(0.40)	5.29	(0.49)	6.23	(0.46)	5.35	(0.35)	5.05	(0.31)	5.84	(0.35)	6.07	(0.48)	5.69	(0.45)	5.69	(0.21)
	150	5.70	(0.49)	5.55	(0.45)	6.36	(0.40)	5.17	(0.51)	5.73	(0.36)	5.54	(0.34)	6.17	(0.41)	5.40	(0.39)	5.40	(0.36)
Popped Balloons	0	6.82	(0.99)	8.27	(0.62)	7.55	(0.68)	8.82	(1.10)	8.73	(0.93)	7.27	(0.94)	7.82	(0.56)	6.91	(0.75)	8.82	(0.68)
	30	7.64	(0.65)	8.27	(0.62)	9.45	(0.79)	8.55	(0.80)	8.55	(0.68)	7.00	(0.73)	8.27	(0.85)	8.45	(0.99)	7.91	(0.66)
	60	7.27	(1.02)	8.45	(0.46)	8.00	(0.55)	8.00	(0.95)	7.45	(0.55)	7.91	(0.93)	8.82	(0.94)	7.91	(0.85)	7.73	(0.58)
	90	6.64	(0.84)	8.36	(0.67)	8.82	(1.05)	7.36	(0.53)	7.91	(0.61)	8.18	(0.61)	7.45	(0.62)	8.36	(0.71)	9.27	(0.93)
	120	7.36	(1.17)	9.82	(0.99)	7.91	(1.10)	7.82	(0.79)	9.27	(1.03)	8.45	(0.92)	7.82	(0.87)	7.45	(0.93)	8.82	(0.47)
	150	7.91	(1.25)	9.27	(0.98)	7.64	(0.84)	8.27	(1.14)	8.18	(0.54)	8.27	(0.90)	7.91	(0.50)	8.09	(1.01)	8.36	(0.67)
CARDIOVASCULAR MEASURES																			
Heart Rate	0	69.36	(2.21)	75.00	(4.75)	74.27	(3.02)	71.27	(2.42)	70.73	(2.69)	67.18	(2.32)	70.18	(2.94)	71.00	(3.60)	68.55	(2.77)
	30	73.73	(2.73)	74.73	(3.08)	76.91	(2.90)	74.73	(3.31)	78.73	(2.49)	71.55	(2.80)	79.36	(3.14)	74.55	(3.06)	72.18	(1.98)
	60	76.55	(2.84)	77.45	(2.88)	76.09	(3.45)	76.36	(3.31)	79.45	(2.45)	73.91	(3.09)	78.55	(2.68)	77.18	(3.17)	77.73	(3.27)
	90	76.91	(3.23)	78.18	(4.43)	77.36	(4.57)	75.36	(3.62)	80.09	(3.63)	80.45	(2.95)	78.36	(3.57)	79.82	(2.83)	80.45	(3.58)
	120	73.82	(2.72)	74.82	(4.28)	80.00	(5.41)	75.18	(3.09)	79.73	(3.38)	76.91	(3.27)	74.27	(3.03)	74.73	(3.25)	78.18	(2.54)
	150	69.09	(1.96)	73.36	(3.54)	77.55	(4.12)	74.55	(3.30)	77.45	(3.49)	72.91	(2.64)	74.09	(2.98)	75.00	(2.78)	77.18	(3.73)
Systolic	0	120.18	(2.95)	120.73	(4.59)	127.36	(3.33)	123.09	(3.75)	125.45	(2.61)	124.00	(2.26)	120.36	(4.14)	125.55	(3.46)	121.18	(1.68)
	30	130.91	(2.58)	129.82	(3.40)	125.09	(3.16)	125.09	(2.63)	129.91	(3.34)	124.18	(2.32)	123.91	(3.56)	121.18	(2.84)	126.00	(1.59)
	60	130.00	(1.99)	127.18	(3.47)	122.55	(3.28)	127.27	(3.26)	126.09	(2.16)	123.91	(2.27)	124.00	(2.01)	122.82	(2.32)	118.73	(2.58)
	90	124.82	(4.89)	122.18	(3.26)	122.45	(3.50)	128.73	(3.34)	127.55	(2.43)	123.82	(3.59)	124.82	(2.45)	127.27	(1.78)	122.82	(2.46)
	120	124.45	(2.61)	121.09	(2.30)	126.36	(3.31)	129.27	(3.26)	124.64	(4.06)	121.45	(2.36)	122.73	(1.84)	125.00	(2.39)	125.00	(2.33)
	150	127.27	(3.59)	125.27	(2.79)	130.55	(2.96)	129.45	(2.08)	124.82	(2.0)	123.82	(2.16)	127.09	(1.13)	129.00	(2.55)	129.00	(2.33)
Diatolic	0	74.91	(2.06)	75.27	(2.59)	79.64	(2.04)	77.55	(3.44)	76.82	(3.12)	77.18	(2.69)	76.55	(2.04)	80.36	(2.73)	77.27	(2.95)
	30	77.09	(4.48)	68.00	(6.20)	74.18	(3.38)	76.64	(2.68)	74.09	(2.56)	73.00	(2.31)	72.00	(2.47)	76.27	(3.53)	75.82	(2.65)
	60	73.91	(2.14)	72.91	(2.34)	72.64	(2.45)	75.82	(1.91)	74.27	(2.83)	74.27	(2.73)	72.36	(3.0)	73.64	(2.16)	75.55	(3.02)
	90	75.45	(2.09)	75.09	(2.76)	75.91	(2.35)	76.82	(2.80)	73.73	(3.29)	75.18	(1.84)	73.45	(2.38)	75.45	(2.51)	73.18	(2.90)
	120	76.09	(2.80)	73.91	(2.19)	76.91	(2.50)	70.00	(5.35)	75.91	(2.09)	71.36	(2.12)	71.36	(2.05)	73.45	(2.33)	72.91	(3.33)
	150	74.55	(2.77)	76.36	(1.76)	77.18	(2.61)	78.91	(2.40)	76.36	(2.59)	69.18	(2.72)	69.00	(3.06)	70.09	(2.64)	73.00	(3.22)
MAP	0	90.18	(2.04)	89.09	(2.36)	93.91	(2.38)	91.36	(3.67)	92.36	(2.85)	92.18	(2.45)	91.64	(2.16)	94.64	(3.62)	90.09	(2.72)
	30	93.00	(4.13)	84.27	(6.68)	89.73	(3.81)	91.73	(3.0)	89.09	(2.30)	88.55	(2.94)	83.18	(2.61)	90.45	(3.72)	94.91	(3.22)
	60	89.00	(2.20)	87.55	(2.97)	88.36	(3.60)	92.82	(3.0)	89.36	(1.95)	87.18	(2.73)	97.55	(8.77)	89.36	(3.01)	88.27	(3.05)
	90	89.27	(3.27)	89.36	(2.31)	91.91	(2.69)	92.36	(2.51)	89.73	(3.64)	90.45	(2.11)	87.55	(2.78)	89.27	(2.97)	87.45	(2.20)
	120	90.55	(2.82)	91.27	(2.11)	92.00	(2.67)	86.27	(5.56)	90.73	(2.93)	87.18	(2.25)	84.55	(2.23)	88.18	(2.56)	85.64	(2.80)
	150	87.00	(3.75)	92.55	(1.56)	91.91	(3.16)	94.00	(2.58)	90.27	(2.20)	82.64	(2.68)	85.82	(3.17)	83.91	(3.11)	87.09	(2.34)

Appendix C. Means and Standard Error Values for Measures Collected in Study 3

DRUG DISCRIMINATION		0 mg PROGESTERONE								100 mg PROGESTERONE							
	TIME	0.00		0.06		0.12		0.25		0.00		0.06		0.12		0.25	
	30	35.19	(9.48)	55.77	(10.67)	54.25	(13.92)	66.46	(15.34)	33.64	(12.57)	27.68	(15.57)	49.57	(15.34)	60.81	(14.78)
	60	16.16	(12.32)	52.10	(15.42)	55.64	(16.49)	76.37	(13.36)	48.39	(17.28)	33.33	(15.46)	64.72	(16.16)	84.98	(11.99)
	90	11.11	(11.79)	46.23	(16.01)	61.43	(17.15)	62.33	(16.27)	22.22	(15.59)	33.02	(15.28)	55.56	(18.63)	100.00	(0.0)
	120	11.11	(11.79)	44.44	(16.42)	48.64	(17.74)	86.01	(11.80)	33.33	(17.68)	28.63	(15.79)	48.64	(17.74)	100.00	(0.0)
	150	11.11	(11.79)	33.26	(15.51)	46.33	(18.10)	100.00	(0.0)	25.16	(15.31)	24.10	(13.64)	48.85	(17.72)	97.53	(2.62)

SELF-REPORT MEASURES			0 mg PROGESTERONE								100 mg PROGESTERONE							
VAS	TIME		0.00		0.06		0.12		0.25		0.00		0.06		0.12		0.25	
Stimulated		0	7.78	(6.07)	5.44	(5.77)	7.67	(5.58)	8.00	(6.70)	8.22	(6.28)	7.44	(6.56)	14.22	(10.03)	12.89	(9.06)
		30	3.89	(4.12)	8.56	(6.53)	6.33	(5.32)	12.78	(9.60)	6.67	(5.76)	12.00	(8.57)	21.00	(9.31)	8.00	(8.49)
		60	3.00	(3.18)	2.11	(2.24)	6.00	(4.64)	13.56	(11.16)	1.78	(1.89)	6.33	(4.0)	21.67	(9.61)	3.22	(2.26)
		90	1.44	(1.53)	2.33	(2.0)	1.33	(1.41)	15.44	(11.56)	1.78	(1.89)	4.00	(3.52)	17.33	(9.80)	3.78	(2.67)
		120	4.11	(4.36)	3.56	(2.49)	0.00	(0.0)	15.67	(12.17)	2.33	(2.47)	3.89	(3.40)	14.56	(7.57)	3.78	(3.29)
		150	4.22	(4.48)	2.56	(1.90)	2.56	(1.85)	14.67	(10.72)	5.56	(5.89)	9.11	(6.34)	11.44	(8.37)	8.89	(6.24)
Sedated		0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	0.22	(0.24)
		30	0.67	(0.71)	0.56	(0.59)	5.89	(3.59)	17.67	(8.99)	1.33	(1.41)	6.89	(6.09)	16.00	(7.27)	12.00	(8.85)
		60	1.56	(1.65)	6.67	(4.10)	6.11	(5.13)	25.56	(11.91)	17.33	(12.77)	16.56	(8.96)	19.22	(7.46)	31.89	(10.06)

SELF-REPORT MEASURES			0 mg PROGESTERONE								100 mg PROGESTERONE							
VAS	TIME		0.00		0.06		0.12		0.25		0.00		0.06		0.12		0.25	
Hungry		0	45.67	(12.30)	24.00	(12.57)	23.00	(10.52)	29.67	(12.87)	40.44	12.84	29.11	(13.07)	25.22	(11.76)	28.67	(11.71)
		30	1.00	(1.06)	0.00	(0.0)	0.00	(0.0)	1.00	(1.06)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		60	0.78	(0.82)	0.00	(0.0)	2.11	(2.24)	7.78	(5.48)	0.00	(0.0)	0.00	(0.0)	6.44	(0.0)	0.00	(0.0)
		90	9.67	(7.38)	0.00	(0.0)	2.44	(1.80)	19.44	(10.46)	0.11	(0.12)	6.89	(7.31)	8.56	(6.84)	5.78	(4.94)
		120	21.22	(7.32)	0.00	(0.0)	6.56	(3.78)	18.11	(10.22)	2.89	(3.06)	9.11	(9.66)	23.89	(6.84)	1.89	(1.87)
		150	23.89	(9.11)	10.22	(5.49)	16.44	(8.85)	17.22	(9.92)	12.22	(7.39)	15.44	(11.72)	23.11	(12.36)	3.33	(2.35)
Thirsty		0	18.67	(8.84)	28.00	(11.44)	16.67	(10.75)	24.89	(11.12)	29.22	(12.0)	25.56	(11.01)	22.56	(13.22)	4.33	(3.61)
		30	9.00	(5.67)	4.11	(2.24)	6.78	(4.85)	0.00	(0.0)	1.78	(1.89)	8.78	(5.26)	13.33	(9.46)	0.00	(0.0)
		60	12.67	(6.76)	2.11	(2.24)	5.44	(4.17)	6.33	(4.69)	2.67	(2.83)	5.78	(4.07)	18.33	(9.46)	0.11	(0.12)
		90	6.67	(4.08)	1.44	(1.53)	5.67	(4.02)	5.67	(4.93)	0.00	(0.0)	2.78	(2.05)	4.89	(11.43)	0.00	(0.0)
		120	6.67	(4.68)	2.11	(2.24)	9.00	(4.81)	5.56	(5.89)	7.33	(4.57)	3.00	(3.18)	9.89	(3.86)	1.89	(2.0)
		150	11.67	(5.45)	5.11	(3.79)	11.67	(6.91)	5.33	(4.80)	7.89	(4.48)	8.89	(7.0)	11.11	(6.24)	3.67	(3.89)
Shaky		0	2.89	(3.06)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	2.89	(3.06)	0.00	(0.0)
		30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.89	(2.0)	0.22	(0.24)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		60	3.33	(2.73)	0.00	(0.0)	0.33	(0.35)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		90	0.22	(0.24)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.67	(1.77)
		120	0.33	(0.35)	0.67	(0.71)	0.00	(0.0)	0.00	(0.0)	0.56	(0.59)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)
		150	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
Jittery		0	0.00	(0.0)	0.00	(0.0)	0.22	(0.24)	1.22	(1.30)	0.00	(0.0)	0.00	(0.0)	3.22	(3.42)	0.11	(0.12)
		30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)
		60	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.33	(0.35)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		90	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	0.00	(0.0)	1.67	(1.77)	0.00	(0.0)	0.11	(0.0)	0.00	(0.0)
		120	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.89	(0.94)	0.00	(0.0)	0.00	(0.12)	0.00	(0.0)
		150	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	6.67	(7.07)
Down		0	2.89	(2.03)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.11	(1.18)
		30	0.00	(0.0)	0.22	(0.16)	0.00	(0.0)	0.00	(0.0)	0.78	(0.82)	0.00	(0.0)	0.44	(0.47)	0.22	(0.24)
		60	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.22	(1.30)	0.00	(0.0)
		90	1.33	(1.41)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.44	(0.47)
		120	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		150	1.89	(1.40)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
Depressed		0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.11	(1.18)
		30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.22	(0.24)	0.00	(0.0)	0.00	(0.0)
		60	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.56	(0.59)	0.00	(0.0)
		90	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.22	(0.24)	0.56	(0.59)
		120	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
		150	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	0.22	(0.24)	0.00	(0.0)
High		0	6.11	(6.35)	5.56	(5.89)	5.56	(5.89)	4.78	(5.07)	5.22	(5.54)	5.67	(6.01)	5.44	(5.77)	5.67	(6.01)
		30	0.00	(0.0)	3.44	(2.47)	4.44	(4.71)	15.89	(10.11)	0.00	(0.0)	1.56	(1.65)	14.67	(9.71)	12.78	(8.77)
		60	0.00	(0.0)	2.33	(2.47)	5.56	(5.89)	22.11	(12.82)	0.00	(0.0)	3.44	(3.65)	12.67	(9.71)	16.56	(8.07)
		90	0.00	(0.0)	4.11	(4.36)	9.22	(5.73)	22.89	(13.11)	0.00	(0.0)	3.67	(3.89)	10.44	(9.27)	19.44	(8.58)
		120	0.00	(0.0)	3.11	(3.30)	3.44	(3.65)	18.89	(12.30)	0.00	(0.0)	0.56	(0.59)	5.56	(8.14)	25.89	(11.01)
		150	0.00	(0.0)	2.00	(1.45)	4.89	(3.52)	18.22	(12.11)	0.00	(0.0)	0.00	(0.0)	4.00	(2.83)	13.89	(8.21)
Euphoric		0	6.11	(6.48)	5.33	(5.66)	5.56	(5.89)	6.11	(6.48)	5.56	(5.89)	5.67	(6.01)	5.78	(6.13)	5.67	(6.01)
		30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	10.22	(10.84)	0.00	(0.0)	0.00	(0.0)	9.44	(10.02)	0.00	(0.0)
		60	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	11.11	(11.79)	0.00	(0.0)	0.00	(0.0)	11.44	(11.75)	8.22	(5.98)
		90	0.00	(0.0)	1.44	(1.53)	1.22	(1.30)	11.11	(11.79)	0.00	(0.0)	0.00	(0.0)	7.67	(7.87)	10.89	(8.92)
		120	0.00	(0.0)	1.11	(1.18)	1.89	(2.0)	11.78	(11.72)	0.00	(0.0)	0.00	(0.0)	4.44	(4.71)	13.33	(9.44)
		150	0.00	(0.0)	1.44	(1.53)	1.67	(1.77)	11.44	(11.75)	0.00	(0.0)	1.67	(1.77)	2.22	(2.36)	7.22	(7.66)
Active		0	41.11	(11.17)	44.00	(11.23)	34.89	(10.07)	45.00	(11.03)	38.67	(10.05)	46.67	(11.81)	48.78	(11.53)	41.22	(10.06)
		30	43.67	(7.49)	41.33	(7.17)	38.44	(9.10)	37.33	(8.57)	35.67	(9.59)	44.89	(7.17)	37.89	(9.63)	38.44	(8.30)
		60	38.67	(7.55)	32.00	(7.17)	35.22	(9.67)	28.22	(8.39)	26.22	(8.97)	38.11	(11.74)	35.44	(9.63)	25.44	(8.09)
		90	38.22	(8.74)	24.56	(8.49)	34.56	(9.92)	32.22	(9.80)	27.00	(9.39)	31.56	(9.80)	27.00	(9.67)	19.56	(7.91)
		120	41.00	(9.70)	32.33	(10.55)	33.44	(10.90)	33.67	(8.34)	31.33	(7.76)	34.67	(8.98)	35.67	(8.35)	23.67	(9.54)
		150	43.78	(10.47)	29.67	(10.61)	32.00	(10.34)	28.22	(7.69)	31.00	(8.06)	40.22	(9.33)	35.44	(9.71)	22.11	(8.45)
Alert		0	52.89	(12.88)	53.78	(12.46)	53.78	(14.59)	60.11	(12.92)	47.89	(13.28)	62.11	(13.42)	54.78	(12.86)	51.67	(12.38)
		30	52.67	(9.57)	48.44	(8.36)	49.22	(11.73)	46.00	(10.51)	46.89	(11.62)	56.67	(9.97)	45.56	(12.44)	46.33	(11.23)
		60	48.11	(10.90)	43.00	(8.30)	45.11	(10.54)	40.78	(8.89)	35.67	(11.03)	48.89	(12.70)	44.00	(12.12)	35.33	(9.18)
		90	51.00	(11.34)	41.11	(10.04)	43.33	(11.76)	45.00	(11.06)	37.56	(10.62)	37.56	(11.13)	42.33	(11.29)	22.22	(8.87)
		120	49.56	(12.15)	44.44	(12.08)	40.67	(11.84)	43.44	(11.01)	41.33	(10.66)	44.33	(10.04)	47.44	(11.78)	34.33	(9.95)
		150	56.44	(13.42)	46.00	(12.24)	45.78	(12.74)	44.44	(11.68)	43.56	(9.96)	51.22	(9.99)	48.44	(11.72)	32.11	(10.38)
Energetic		0	39.56	(11.05)	48.11	(12.90)	30.67	(12.70)	45.33	(12.53)	31.11	(9.74)	49.44	(12.69)	44.44	(11.72)	39.78	(12.84)
		30	42.78	(8.66)	42.78	(9.70)	30.22	(9.99)	33.33	(9.18)	33.89	(10.16)	47.33	(9.06)	36.56	(11.75)	34.11	(11.15)
		60	40.11	(10.10)	31.56	(10.02)	35.00	(12.45)	33.33	(10.62)	23.67	(9.31)	40.00	(11.95)	26.44	(10.55)	21.33	(8.84)
		90	39.11	(10.12)	28.89	(11.02)	33.56	(13.01)	26.00	(10.54)	22.00	(8.86)	28.56	(11.51)	24.89	(10.42)	28.33	(10.23)
		120	41.11	(11.50)	26.11	(11.65)	27.89	(11.29)	29.67	(10.72)	26.00	(9.98)	33.67	(12.24)	29.44	(11.53)	20.11	(10.07)
		150	43.33	(11.82)	28.33	(12.78)	31.67	(12.82)	26.44	(9.09)	27.00	(9.40)	38.22	(12.47)	34.00	(11.88)	24.33	(11.14)

		0 mg PROGESTERONE								100 mg PROGESTERONE							
SELF-REPORT MEASURES																	
VAS	**TIME**	**0.00**		**0.06**		**0.12**		**0.25**		**0.00**		**0.06**		**0.12**		**0.25**	
Rush	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
	30	8.33	(7.07)	1.22	(6.03)	0.78	(0.82)	20.33	(13.97)	5.11	(5.42)	11.11	(8.49)	22.00	(12.43)	22.22	(15.59)
	60	6.89	(5.60)	8.56	(6.03)	0.89	(0.94)	29.67	(16.09)	16.22	(12.34)	26.11	(15.35)	19.89	(12.43)	26.56	(15.01)
	90	4.00	(4.11)	6.22	(6.60)	5.78	(4.35)	27.22	(14.82)	5.67	(4.02)	13.11	(7.54)	23.11	(14.05)	36.22	(16.17)
	120	2.44	(2.59)	0.67	(0.71)	9.67	(8.14)	23.22	(13.65)	0.44	(0.47)	8.11	(8.08)	14.00	(13.39)	26.11	(15.35)
	150	0.00	(0.0)	0.00	(0.0)	7.44	(7.90)	23.67	(12.89)	0.00	(0.0)	7.89	(6.26)	8.56	(9.07)	24.33	(13.63)
Performance Impaired	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
	30	0.44	(0.47)	3.22	(3.42)	6.00	(5.61)	23.00	(11.96)	0.00	(0.0)	4.56	(3.46)	21.33	(9.57)	23.22	(13.25)
	60	5.56	(5.89)	8.33	(4.53)	9.33	(6.61)	33.22	(11.42)	18.00	(13.07)	14.78	(11.94)	27.89	(8.03)	36.11	(13.71)
	90	5.78	(6.13)	10.67	(7.73)	10.00	(5.41)	28.44	(13.49)	10.00	(10.47)	12.33	(11.69)	32.22	(11.96)	46.78	(12.89)
	120	5.44	(5.77)	15.33	(8.91)	11.89	(8.51)	28.11	(11.20)	4.67	(4.95)	13.78	(9.80)	16.44	(11.78)	43.33	(12.89)
	150	1.11	(1.18)	10.67	(9.71)	7.11	(5.07)	22.11	(9.34)	2.56	(2.71)	3.67	(3.89)	14.00	(8.85)	36.56	(14.95)
Performance Improved	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
	30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.22	(1.30)	0.00	(0.0)	0.11	(0.12)	1.78	(1.89)	0.00	(0.0)
	60	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	5.56	(4.92)	0.00	(0.0)	0.00	(0.0)	7.89	(6.03)	3.33	(3.28)
	90	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	5.44	(4.81)	0.00	(0.0)	0.00	(0.0)	1.89	(2.0)	2.22	(2.36)
	120	0.00	(0.0)	5.89	(6.25)	0.11	(0.12)	4.67	(3.57)	0.33	(0.35)	0.00	(0.0)	0.00	(0.0)	5.11	(3.69)
	150	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	3.00	(2.08)	0.00	(0.0)	0.00	(0.0)	1.11	(1.18)	3.11	(3.30)
Drug Effect	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	0.22	(0.24)	0.00	(0.0)	0.00	(0.0)
	30	1.78	(1.89)	5.89	(9.07)	11.33	(7.39)	33.11	(14.87)	1.56	(1.65)	8.44	(5.93)	26.22	(11.70)	30.22	(13.54)
	60	3.67	(3.89)	18.44	(9.07)	19.33	(8.99)	44.33	(15.02)	20.22	(13.93)	22.44	(12.99)	37.89	(11.70)	46.56	(13.21)
	90	7.11	(7.54)	22.22	(9.09)	19.00	(7.58)	43.89	(15.49)	21.33	(13.50)	25.33	(13.13)	34.78	(12.85)	58.89	(11.60)
	120	6.00	(6.36)	20.00	(7.63)	20.56	(8.04)	45.00	(12.57)	12.22	(7.96)	17.00	(9.25)	19.44	(11.66)	50.44	(12.95)
	150	2.44	(2.59)	19.78	(8.79)	7.56	(5.02)	40.33	(10.70)	3.11	(3.30)	9.67	(5.70)	17.22	(7.65)	54.00	(12.92)
Good Drug Effect	0	0.11	(0.12)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
	30	5.56	(5.89)	0.00	(0.0)	2.33	(2.47)	27.33	(15.51)	0.00	(0.0)	7.67	(8.13)	17.56	(11.83)	18.89	(12.30)
	60	6.22	(6.60)	6.33	(6.72)	0.56	(0.59)	27.11	(15.47)	8.78	(9.18)	14.56	(11.89)	18.78	(12.0)	24.44	(12.33)
	90	5.33	(5.66)	8.00	(6.93)	5.33	(3.75)	27.67	(15.57)	8.00	(8.49)	12.44	(11.69)	23.67	(12.76)	27.89	(12.92)
	120	7.00	(7.42)	16.56	(10.90)	4.56	(3.40)	30.00	(16.07)	6.44	(6.84)	11.89	(11.71)	13.33	(7.90)	29.78	(12.87)
	150	6.33	(6.72)	8.33	(7.38)	3.56	(3.77)	26.00	(14.26)	0.00	(0.0)	8.56	(6.92)	9.89	(7.53)	25.44	(15.18)
Bad Drug Effect	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)
	30	0.00	(0.0)	2.11	(2.71)	5.22	(5.54)	9.89	(6.97)	0.00	(0.0)	0.00	(0.0)	2.89	(3.06)	10.67	(6.33)
	60	0.00	(0.0)	2.56	(2.71)	3.22	(3.42)	12.89	(9.18)	0.00	(0.0)	0.11	(0.12)	4.44	(3.06)	10.33	(7.26)
	90	0.11	(0.12)	2.89	(3.06)	3.67	(3.89)	5.89	(5.36)	0.00	(0.0)	0.00	(0.0)	12.67	(4.58)	9.33	(6.58)
	120	0.00	(0.0)	7.89	(6.34)	0.11	(0.12)	9.00	(6.49)	0.00	(0.0)	0.00	(0.0)	10.22	(9.63)	11.44	(8.03)
	150	0.00	(0.0)	1.33	(1.41)	6.44	(6.84)	9.67	(7.31)	0.00	(0.0)	0.00	(0.0)	5.11	(5.42)	15.78	(9.36)
Like Drug Effect	0	2.22	(2.36)	0.00	(0.0)	4.78	(5.07)	1.67	(1.64)	4.33	(4.60)	5.67	(6.01)	11.78	(8.31)	6.89	(7.18)
	30	9.33	(6.70)	2.78	(12.43)	5.00	(3.52)	33.56	(15.09)	7.00	(5.46)	14.22	(8.33)	15.22	(10.63)	25.33	(13.84)
	60	8.89	(6.53)	19.22	(12.43)	3.00	(3.18)	37.11	(16.88)	17.22	(11.25)	22.11	(11.87)	28.33	(10.63)	30.00	(12.88)
	90	7.56	(8.01)	19.89	(11.93)	7.33	(4.08)	29.11	(15.07)	14.00	(11.25)	20.00	(12.0)	29.89	(13.35)	38.78	(14.18)
	120	9.67	(7.19)	17.89	(13.01)	10.22	(7.04)	33.44	(15.12)	8.89	(7.17)	19.89	(11.60)	24.44	(13.37)	27.67	(13.05)
	150	8.33	(6.31)	14.56	(9.51)	14.11	(9.64)	31.44	(13.92)	7.22	(5.46)	13.22	(7.21)	16.78	(7.64)	35.44	(15.01)
Willing to Take Again	0	5.56	(5.76)	14.56	(10.53)	5.33	(5.66)	5.44	(5.77)	5.00	(5.30)	5.56	(5.63)	5.33	(5.66)	5.22	(5.54)
	30	43.89	(13.93)	38.22	(14.90)	38.00	(15.13)	52.22	(16.42)	28.56	(14.36)	37.00	(14.62)	43.00	(14.76)	41.56	(15.20)
	60	43.67	(13.73)	47.11	(15.37)	37.44	(14.73)	49.33	(16.01)	39.56	(16.0)	44.33	(15.47)	39.78	(15.37)	52.00	(14.15)
	90	46.33	(14.42)	49.78	(15.40)	42.00	(13.69)	59.67	(15.17)	37.89	(15.52)	40.56	(15.67)	44.78	(14.28)	53.00	(15.24)
	120	34.33	(13.72)	48.00	(16.03)	46.78	(13.34)	57.56	(15.42)	34.67	(13.94)	42.11	(15.73)	34.11	(13.12)	57.11	(13.62)
	150	43.44	(14.02)	47.44	(15.80)	30.67	(14.20)	47.22	(15.49)	32.78	(13.71)	35.00	(13.83)	31.78	(13.60)	48.33	(15.64)
Pay For Drug	0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)
	30	2.33	(2.47)	0.00	(11.77)	0.00	(0.0)	22.22	(15.59)	0.00	(0.0)	8.44	(8.82)	10.67	(11.31)	13.89	(11.79)
	60	1.44	(1.40)	11.22	(11.77)	0.00	(0.0)	30.78	(16.49)	11.11	(11.79)	11.33	(11.76)	11.11	(11.31)	14.89	(11.92)
	90	4.00	(4.24)	12.33	(11.69)	3.11	(2.29)	22.44	(15.55)	10.11	(10.72)	11.11	(11.79)	11.11	(11.79)	29.67	(16.09)
	120	2.11	(2.24)	12.56	(11.68)	9.56	(8.23)	22.22	(15.59)	5.22	(5.54)	11.11	(11.79)	8.89	(11.79)	18.33	(13.23)
	150	1.00	(1.06)	12.11	(11.70)	1.22	(1.30)	20.33	(14.34)	2.78	(2.95)	6.33	(5.22)	6.78	(4.76)	22.11	(15.41)
Irregular/Racing HR	0	6.22	(6.60)	5.67	(6.01)	5.67	(5.75)	5.11	(5.42)	5.56	(5.89)	5.44	(5.77)	5.44	(5.77)	5.67	(6.01)
	30	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
	60	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	2.56	(2.71)	0.00	(0.0)	0.22	(0.24)	0.22	(0.24)	1.78	(1.76)
	90	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.44	(0.36)	1.67	(1.77)
	120	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	1.00	(1.06)
	150	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.11	(0.12)	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)	0.89	(0.94)
ARS																	
Sedative	0	4.33	(1.36)	2.89	(1.43)	4.56	(1.40)	2.67	(1.02)	4.56	(1.71)	3.78	(1.31)	3.67	(1.09)	3.89	(1.30)
	30	4.89	(1.64)	4.44	(1.61)	6.89	(1.51)	12.11	(3.76)	5.11	(1.35)	6.44	(2.31)	11.00	(2.80)	9.89	(2.67)
	60	5.00	(2.22)	7.89	(1.88)	8.44	(2.59)	13.11	(3.64)	9.11	(3.71)	12.44	(5.34)	11.78	(2.61)	18.33	(4.63)
	90	6.11	(2.56)	8.33	(2.37)	9.33	(2.73)	14.11	(4.21)	8.56	(2.54)	10.22	(4.20)	12.11	(1.96)	20.00	(5.07)
	120	5.89	(2.42)	9.44	(3.06)	11.33	(3.81)	13.44	(3.92)	6.89	(1.56)	9.11	(3.56)	10.89	(2.74)	19.44	(4.29)
	150	3.89	(1.01)	9.56	(3.08)	9.11	(3.17)	12.56	(2.98)	5.78	(1.39)	6.33	(1.39)	9.11	(2.88)	17.11	(4.03)

			0 mg PROGESTERONE				100 mg PROGESTERONE			
PERFORMANCE MEASURES										
DSST	**TIME**	**0.00**	**0.06**	**0.12**	**0.25**	**0.00**	**0.06**	**0.12**	**0.25**
Total Trials	0	82.56 (2.95)	83.22 (4.30)	82.44 (3.41)	84.00 (3.73)	83.22 (3.61)	83.33 (3.56)	83.33 (3.83)	82.78 (4.02)
	30	83.67 (2.71)	81.89 (3.38)	80.44 (3.14)	77.89 (4.90)	82.89 (3.17)	82.56 (3.22)	78.78 (3.66)	77.89 (3.29)
	60	84.22 (2.75)	81.89 (3.81)	78.56 (3.20)	72.44 (4.69)	82.11 (2.67)	81.67 (2.91)	76.67 (3.70)	70.56 (5.77)
	90	82.22 (3.02)	81.06 (3.82)	79.11 (4.03)	72.33 (4.12)	81.89 (2.97)	79.67 (2.82)	79.33 (3.09)	70.22 (4.01)
	120	84.44 (2.82)	81.00 (4.11)	79.89 (3.74)	73.11 (4.14)	83.78 (2.86)	82.44 (2.85)	80.22 (3.27)	72.00 (4.21)
	150	84.33 (2.99)	82.78 (4.22)	79.67 (3.43)	75.56 (3.68)	84.22 (3.29)	82.78 (3.69)	81.22 (3.15)	74.00 (4.19)
Correct	0	79.22 (2.78)	80.00 (4.06)	79.67 (3.77)	79.11 (3.59)	78.44 (3.45)	81.44 (3.58)	80.78 (3.53)	78.78 (4.14)
	30	80.33 (2.35)	77.33 (3.54)	76.89 (2.96)	73.44 (4.66)	78.89 (2.88)	78.89 (3.01)	74.67 (3.28)	73.33 (2.97)
	60	80.78 (2.54)	78.00 (3.54)	74.11 (2.29)	68.44 (4.57)	77.78 (2.36)	77.33 (3.11)	72.56 (3.28)	65.78 (5.73)
	90	78.11 (2.43)	77.11 (3.14)	75.89 (3.70)	66.78 (3.80)	76.78 (2.55)	75.78 (3.13)	73.89 (3.50)	65.78 (3.45)
	120	81.33 (3.10)	76.89 (3.65)	77.89 (3.59)	69.00 (3.50)	79.56 (2.48)	78.89 (2.87)	74.44 (2.94)	65.22 (4.20)
	150	80.78 (3.08)	79.44 (3.95)	76.00 (3.50)	71.67 (3.49)	79.00 (3.26)	79.11 (3.15)	77.78 (2.58)	68.11 (4.72)
Errors	0	3.33 (0.81)	3.22 (1.18)	2.78 (0.75)	4.89 (1.01)	4.78 (0.95)	1.89 (0.72)	2.56 (1.03)	4.00 (0.92)
	30	3.33 (0.77)	4.56 (1.12)	3.56 (0.87)	4.44 (1.21)	4.00 (0.83)	3.67 (0.77)	4.11 (1.02)	4.56 (1.39)
	60	3.44 (1.02)	3.89 (1.08)	4.44 (1.28)	4.00 (1.33)	4.33 (0.92)	4.33 (0.85)	4.11 (1.48)	4.78 (1.03)
	90	4.11 (1.23)	3.94 (1.08)	3.22 (0.88)	5.56 (1.61)	5.11 (0.96)	3.89 (1.37)	5.44 (1.67)	4.44 (0.95)
	120	3.11 (0.82)	4.11 (1.17)	2.00 (0.61)	4.11 (1.08)	4.22 (0.86)	3.56 (0.73)	5.78 (1.59)	6.78 (1.42)
	150	3.56 (0.89)	3.33 (0.85)	3.67 (1.17)	3.89 (1.05)	5.22 (1.62)	3.67 (1.0)	3.44 (1.46)	5.89 (1.67)
Proportion Correct	0	0.96 (0.01)	0.96 (0.01)	0.96 (0.01)	0.94 (0.01)	0.94 (0.01)	0.98 (0.01)	0.97 (0.01)	0.95 (0.01)
	30	0.96 (0.01)	0.95 (0.01)	0.96 (0.01)	0.94 (0.01)	0.95 (0.01)	0.96 (0.01)	0.95 (0.01)	0.94 (0.02)
	60	0.96 (0.01)	0.95 (0.01)	0.95 (0.01)	0.94 (0.02)	0.95 (0.01)	0.95 (0.01)	0.95 (0.02)	0.93 (0.02)
	90	0.95 (0.01)	0.95 (0.01)	0.96 (0.01)	0.92 (0.02)	0.94 (0.01)	0.95 (0.02)	0.93 (0.02)	0.94 (0.01)
	120	0.96 (0.01)	0.95 (0.01)	0.98 (0.01)	0.95 (0.01)	0.95 (0.01)	0.96 (0.01)	0.93 (0.02)	0.91 (0.02)
	150	0.96 (0.01)	0.96 (0.01)	0.95 (0.02)	0.95 (0.01)	0.94 (0.02)	0.96 (0.01)	0.96 (0.02)	0.92 (0.03)
BART									
Earning	0	6.20 (0.50)	5.94 (0.34)	6.31 (0.40)	6.60 (0.22)	5.62 (0.53)	5.57 (0.29)	6.30 (0.63)	5.90 (0.42)
	30	5.42 (0.45)	5.93 (0.41)	5.32 (0.42)	6.11 (0.48)	5.27 (0.32)	5.78 (0.41)	6.45 (0.42)	4.90 (0.35)
	60	5.70 (0.38)	5.91 (0.51)	6.16 (0.29)	5.67 (0.51)	5.38 (0.41)	6.29 (0.42)	6.09 (0.43)	5.04 (0.38)
	90	6.39 (0.57)	6.25 (0.40)	5.71 (0.45)	6.39 (0.15)	5.84 (0.53)	6.12 (0.28)	6.06 (0.51)	5.05 (0.25)
	120	6.08 (0.40)	5.29 (0.49)	6.23 (0.46)	6.07 (0.48)	5.35 (0.35)	5.05 (0.31)	5.84 (0.35)	5.69 (0.45)
	150	5.70 (0.49)	5.55 (0.45)	6.36 (0.40)	6.17 (0.41)	5.17 (0.51)	5.73 (0.36)	5.54 (0.34)	5.40 (0.39)
Popped Balloons	0	6.82 (0.99)	8.27 (0.62)	7.55 (0.68)	7.82 (0.56)	8.82 (1.10)	8.73 (0.93)	7.27 (0.94)	6.91 (0.75)
	30	7.64 (0.65)	8.27 (0.62)	9.45 (0.79)	8.27 (0.85)	8.55 (0.80)	8.55 (0.68)	7.00 (0.73)	8.45 (0.99)
	60	7.27 (1.02)	8.45 (0.46)	8.00 (0.55)	8.82 (0.94)	8.00 (0.95)	7.45 (0.55)	7.91 (0.93)	7.91 (0.85)
	90	6.64 (0.84)	8.36 (0.67)	8.82 (1.05)	7.45 (0.62)	7.36 (0.53)	7.91 (0.61)	8.18 (0.61)	8.36 (0.71)
	120	7.36 (1.17)	9.82 (0.99)	7.91 (1.10)	7.82 (0.87)	7.82 (0.79)	9.27 (1.03)	8.45 (0.92)	7.45 (0.93)
	150	7.91 (1.25)	9.27 (0.98)	7.64 (0.84)	7.91 (0.50)	8.27 (1.14)	8.18 (0.54)	8.27 (0.90)	8.09 (1.01)
CARDIOVASCULAR MEASURES									
Heart Rate	0	75.11 (5.69)	76.89 (3.63)	73.67 (4.37)	78.33 (3.19)	76.22 (3.45)	76.44 (4.04)	79.89 (4.73)	78.22 (4.58)
	30	76.11 (4.22)	75.33 (4.56)	75.44 (6.58)	80.11 (4.40)	75.22 (3.32)	74.67 (4.11)	79.22 (5.0)	75.56 (4.54)
	60	79.22 (3.84)	77.22 (4.47)	76.22 (5.38)	78.22 (3.94)	75.78 (2.52)	73.22 (2.89)	80.00 (4.19)	80.67 (4.68)
	90	80.00 (4.59)	76.89 (4.26)	76.78 (5.56)	81.56 (3.89)	73.89 (3.08)	76.22 (3.77)	77.11 (4.03)	83.00 (5.29)
	120	74.11 (4.54)	75.22 (4.57)	75.89 (3.84)	78.44 (3.95)	74.11 (4.33)	74.11 (4.22)	77.00 (5.16)	78.67 (4.02)
	150	72.33 (3.90)	74.67 (4.30)	74.67 (3.0)	76.00 (4.05)	71.44 (3.0)	72.78 (4.34)	73.44 (4.49)	78.67 (4.84)
Systolic	0	126.89 (6.88)	127.78 (3.49)	127.56 (6.59)	128.67 (5.0)	123.44 (4.0)	124.11 (3.76)	126.22 (5.01)	125.22 (5.94)
	30	129.00 (6.51)	127.67 (5.99)	124.11 (3.65)	124.22 (5.75)	125.67 (6.20)	124.78 (4.17)	128.22 (3.06)	124.22 (4.66)
	60	134.56 (6.17)	129.89 (5.99)	123.89 (2.97)	124.44 (6.01)	123.33 (5.41)	124.78 (3.76)	125.00 (3.06)	129.11 (6.99)
	90	123.00 (5.36)	127.78 (4.75)	125.56 (2.42)	121.44 (6.62)	121.33 (5.31)	122.33 (6.60)	125.67 (3.95)	123.33 (6.95)
	120	127.78 (6.17)	123.44 (3.96)	122.33 (4.95)	126.44 (6.32)	123.00 (5.41)	124.89 (5.06)	129.56 (4.63)	120.78 (5.43)
	150	125.44 (6.68)	130.56 (5.33)	126.33 (4.27)	130.00 (5.71)	126.67 (5.79)	125.56 (4.07)	126.11 (4.14)	123.78 (5.15)
Diatolic	0	79.22 (4.10)	77.89 (3.30)	76.56 (4.51)	84.11 (3.62)	77.33 (2.99)	77.11 (1.92)	75.78 (3.04)	79.11 (3.53)
	30	79.67 (3.68)	75.11 (3.22)	80.22 (2.99)	79.44 (3.20)	77.44 (3.06)	76.44 (2.67)	77.33 (2.56)	75.89 (4.04)
	60	77.56 (3.15)	76.33 (3.46)	78.22 (3.30)	75.67 (3.69)	74.78 (2.95)	73.56 (3.11)	77.00 (2.65)	74.33 (3.61)
	90	77.56 (3.11)	76.78 (3.36)	77.56 (2.78)	77.56 (2.73)	74.33 (2.90)	75.44 (3.39)	75.33 (3.07)	75.11 (4.86)
	120	74.22 (4.0)	74.78 (3.88)	78.33 (2.0)	77.56 (3.19)	72.56 (3.29)	75.78 (3.07)	81.11 (4.24)	73.00 (3.47)
	150	80.22 (3.73)	77.67 (3.67)	78.78 (2.78)	77.78 (2.92)	74.00 (3.29)	77.44 (2.54)	81.44 (3.57)	65.67 (5.31)
MAP	0	97.11 (5.62)	93.22 (4.16)	92.00 (4.59)	99.00 (4.83)	90.56 (3.22)	94.22 (4.43)	88.56 (4.38)	94.78 (4.31)
	30	99.56 (5.73)	92.67 (4.14)	95.00 (3.19)	94.22 (3.70)	92.11 (3.89)	90.56 (3.15)	92.78 (2.66)	91.56 (5.50)
	60	92.89 (3.58)	91.00 (4.11)	94.67 (2.57)	90.56 (4.93)	88.00 (3.62)	90.00 (3.06)	93.33 (2.47)	92.00 (4.84)
	90	91.78 (4.25)	92.89 (6.09)	93.33 (3.90)	92.89 (3.89)	90.00 (4.34)	87.56 (3.58)	93.33 (3.15)	89.22 (5.17)
	120	90.11 (6.62)	88.33 (4.78)	94.78 (3.07)	94.44 (3.18)	87.22 (3.52)	91.89 (3.99)	97.11 (3.96)	87.44 (4.34)
	150	95.44 (3.77)	93.44 (3.71)	93.78 (3.28)	93.56 (4.43)	87.78 (3.82)	90.44 (2.83)	99.67 (4.84)	93.11 (6.39)

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