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Maternal depression and neurobehavior in newborns prenatally exposed to methamphetamine

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Abstract

Background—The effects of maternal depression on neonatal neurodevelopment in MA exposed neonates have not been well characterized.

Objective—To determine the neurobehavioral effects of maternal depressive symptoms on neonates exposed and not exposed to methamphetamine (MA) using the NICU Network Neurobehavioral Scale (NNNS).

Design—The purpose of the IDEAL study is to determine the effects of prenatal MA exposure on child outcome. IDEAL screened 13,808 subjects, 1632 were eligible and consented and 176 mothers were enrolled. Only biological mothers with custody of their child at the one-month visit ($n=50$ MA; $n=86$ comparison) had the Addiction Severity Index (ASI) administered. The NNNS was administered to the neonate by an examiner blinded to MA exposure within the first five days of life. General Linear Models tested the effects of maternal depression and prenatal MA exposure on NNNS outcomes, with and without covariates. Significance was accepted at $p<.05$.

Results—After adjusting for covariates, regardless of exposure status, maternal depressive symptoms were associated with lower handling and arousal scores, elevated physiological stress scores and an increased incidence of hypotonicity. When adjusting for covariates, MA exposure was associated with lower arousal and higher lethargy scores.

Conclusions—Maternal depressive symptoms are associated with neurodevelopmental patterns of decreased arousal and increased stress. Prenatal MA exposure combined with maternal depression was not associated with any additional neonatal neurodevelopmental differences.

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Keywords

Prenatal exposure; Neurodevelopment; Drugs; Depression

1. Introduction

According to the 2005 National Survey on Drug Use and Health (NSDUH), an estimated 512,000 people in the United States over the age of 12 used methamphetamine the previous month, 192,000 being new users [58]. Additionally, an estimated ten million people have used methamphetamine at least once in their lifetime [58]. Methamphetamine (MA) use has been associated with an increase in high risk behavior resulting in a rise in HIV transmission [8] and numerous other health problems including seizures, weight loss, paranoia and depression [57]. The NSDUH estimated that 3.9% of pregnant women ages 15 to 44 years reported using illicit drugs in the past month [58]. To date, little is known regarding the effects of prenatal MA exposure on the developing child.

The effects of prenatal MA exposure on the developing fetus have not been well characterized. Fetal growth restriction, and decreased arousal, increased stress, and poor quality of movement on the NICU Network Neurobehavioral Scale (NNNS) has been reported in MA-exposed neonates [52,55]. In children exposed to prenatal amphetamine, Billing and colleagues found lower IQ test scores at 4 years of age compared to the unexposed children (103 vs. 110, respectively) [7]. These data reported in older children are limited by small sample size, lack of a control group and confounding with other prenatal drug exposures.

The NSDUH reported that illicit drug use was higher among adults with serious psychological distress as compared to those without (26.9% vs. 12.1%, respectively) [58]. Zweben and colleagues reported 34% of MA-using women displayed depressive symptoms upon entry into drug treatment programs [60]. Positron emission tomography scans have shown MA users have a reduction in dopamine transporters. Symptoms related to reduced dopamine transporters mimic those of depression [50,60]. In addition, Volkow and colleagues found that depressive symptoms are not only present after an episode of MA use, but can persist for several months after abstinence [59]. Since depression is highly correlated with MA use, the depression associated with MA use during pregnancy may be associated with adverse effects in exposed infants.

Depression during pregnancy is associated with less spousal support [43], increased anger and anxiety episodes [21,22], and more stressors in the areas of work, health, family, friends and environment [12]. Antepartum depression is associated with less prenatal care, more obstetric complications, preterm labor, less weight gain during pregnancy, and increased use of drugs, alcohol and tobacco compared to mothers with little or no prenatal depression [2,22,23,29, 48,56]. Field and colleagues found increased fetal activity, physiological activity and fetal heart rates, and delayed growth in fetuses of mothers who are depressed [23]. Neonates of mothers who were depressed during pregnancy are at greater risk for low birthweight (<2500 g) and being small for gestational age (<10th percentile) [23]. These growth impairments have been shown to continue throughout the first year of life [23,30] potentially leading to long term health complications in the child.

The effect of prenatal depression on infants has also been examined. Hurley and colleagues found that WIC participants with depressive symptomatology were more likely to exhibit forceful, indulgent and uninvolved feeding style scores [31]. In addition, the increased fetal cortisol levels associated with maternal depression have been associated with an inhibited or fearful temperament and less positive affect after birth [23,30]. Prenatal depression is also

associated with less optimal infant scores for orientation, reflexes, excitability and withdrawal on the Brazelton Neonatal Behavioral Assessment Scale [23]. The underlying mechanisms causing the differences in neonates of depressed mothers during the prepartum period have been evaluated. Depressed women have higher cortisol and norepinephrine levels and lower dopamine levels than non-depressed women, creating an imbalance in the chemicals in the prenatal environment [23]. Cortisol is involved with the complex pathways of hypothalamic-pituitary axis (HPA) and sympathoadrenal dysregulation. It has been hypothesized that elevated cortisol may cross the placenta and affect fetal growth by dysregulating fetal autonomic nervous system activity which may lead to fetal HPA reprogramming and altered nervous system development [23,38]. In addition, higher norepinephrine levels affect the cardiovascular system of the neonate [23]. Diego and colleagues found that newborns of mothers with depressive symptoms had elevated urine cortisol and norepinephrine levels and lower dopamine levels, mimicking the biochemical profile of their depressed mothers [2,23]. In addition, infants in the prepartum group demonstrated greater relative right frontal electroencephalogram (EEG) asymmetry which had been found to be associated with a disposition towards behavioral inhibition and negative affect later in life [13,14,25]. These findings suggest maternal depression can influence an infant's neurobehavior starting in utero.

Although the effects of prenatal MA use during pregnancy and the increased incidence of depressive symptoms associated with MA use have been reported, no prior research has investigated the impact of maternal depressive symptoms on the neurodevelopment of neonates exposed to MA during pregnancy. The Infant Development, Environment, and Lifestyle (IDEAL) study is a prospective longitudinal study investigating the effects of prenatal MA exposure. To our knowledge, this is the first study to look at the effects of maternal depressive symptoms on neurodevelopment in MA exposed neonates. We hypothesized that maternal depressive symptoms would be associated with differences in neonatal neurodevelopment. Additionally, we hypothesized that MA use and maternal depression in combination would be associated with poorer neonatal neurodevelopment relative to infants born to non-depressed MA using women.

2. Methods

2.1. Study design

Since the purpose of the IDEAL study is to determine the effects of prenatal MA exposure on child outcome, clinical sites were chosen to participate in specific geographical areas known to have high MA use. The cities chosen were Los Angeles, CA; Des Moines, IA; Tulsa, OK; and Honolulu, HI. The study was approved by the Institutional Review Boards at all participating sites. Prior to initiation of recruitment, personnel from all sites met for a week-long training session to standardize procedures. Re-training is provided on an ongoing basis at each site [4]. The recruitment period lasted for two years; we present neonatal neurodevelopmental findings in the cohort recruited through the end of the first year.

A National Institute on Drug Abuse Certificate of Confidentiality was obtained for the project that assured confidentiality of information regarding the subjects' drug use, superseding mandatory reporting of illegal substance use. The certificate was explained to the mother during the recruitment and informed consent process, including the condition that the certificate did not exclude reporting of evidence of child abuse or neglect.

2.2. Participants

IDEAL screened 13,808 subjects at the time of the infant's birth. At the four sites, 1632 (11.8%) were eligible and consented, but only mothers with prenatal MA use and their matched controls were enrolled ($N=176$). The exclusion criteria for the mother were: age <18; opiate, LSD, PCP

or cocaine only use during pregnancy; institutionalized for retardation or emotional disorders; overtly psychotic or a documented history of psychosis; non-English speaking. Exclusion criteria for children were: critically ill and unlikely to survive; multiple birth; major life threatening congenital anomaly; documented chromosomal abnormality associated with mental or neurological deficiency; overt TORCH infection; sibling previously enrolled in the IDEAL study. A history of maternal alcohol, marijuana, and/or tobacco use during the pregnancy was considered background variables in both the exposed and unexposed groups.

All mothers in the MA exposed group were invited to participate in the follow-up study. Follow-up visits were performed on 84 enrolled exposed subjects and 92 unexposed controls; groups were matched based on race, birth weight, maternal education, and type of insurance. Since we are analyzing the effect of prenatal depression at the one-month visit, only biological mothers ($N=136$) with custody of their child at the one-month visit were included in the analysis. Exposed subjects ($n=50$) were identified by maternal report of MA use during the pregnancy based on the hospital interview and/or GC/MS confirmation of amphetamine and metabolites in infant meconium. Unexposed subjects ($n=86$) were defined as denial of MA use during this pregnancy and a negative GC/MS for amphetamine and metabolites.

2.3. Procedures

After consent was obtained, a medical chart review and a Recruitment Lifestyle Interview [5, 36] was performed to acquire information about prenatal substance use (MA, cocaine, alcohol, opiates, tobacco, marijuana, amphetamines, heroin, hashish, ecstasy, benzodiazepines, barbiturates, LSD, PCP), maternal characteristics (race, type of insurance, # of prenatal visits, education level, weight, weight gain during pregnancy, height, and age), and newborn characteristics (medical history, gender, birth weight, length, head circumference, gestational age, and APGAR scores). Meconium was collected in the nursery on all consented infants. Information on the collection procedures and analysis of the meconium samples was published previously [54].

Depression status was obtained by trained staff at the 1-month study visit using the Addiction Severity Index (ASI). The ASI is a semi-structured interview designed to address seven potential problem areas in substance abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status [40]. The ASI takes approximately 45 min to administer to the mothers and was deferred to the one month session in order to accommodate the mothers' need for rest in the immediate postpartum period and the limited window of time during the initial recruitment period.

The ASI was used to identify participants who had "experienced serious depression" in the past 30 days as well as those who had "a lifetime history of depression" [40,49]. The depressive symptomatology group was defined as subjects who reported lifetime depression and demonstrated either of the following: serious depression more than two weeks in the last 30 days or at least one depressive symptom over the preceding 30 days. Symptoms include a score of one ("Yes") on the following items in the ASI: experiencing serious anxiety/tension during the last 30 days; experienced psychological or emotional problems for 4 or more days during the last 30 days; troubled by or bothered by psychological or emotional problems in the past 30 days; treatment for these psychological or emotional problem is important to you now [40].

The ASI has been found to discriminate depressed from non-depressed addicts with a sensitivity of .83 and a specificity of .55 as compared to other semi-structured interview diagnoses of depression [47]. The ASI has previously been used as a screening tool for depression in pregnant and postpartum women [40,49]. Relevant to this study, both a lifetime history of depression and postpartum depression have been found to be correlated with the

incidence of depression during pregnancy [3,6,17,42,44,48] and both of these variables are measured in the ASI.

The NNNS exam was administered to the neonate within the first five days of birth by certified examiners masked to MA exposure status. The NNNS provides an assessment of neurological, behavioral, and stress/abstinence neurobehavioral function [37]. The neurological component includes active and passive tone, primitive reflexes, and items that reflect the integrity of the central nervous system and maturity of the infant. The behavior component is based on items from the Neonatal Behavioral Assessment Scale [10] modified to be sensitive to putative drug effects. The stress/abstinence component is a checklist of “yes” or “no” items organized by organ system based primarily on the work of Finnegan [24]. The NNNS is a standardized neurobehavioral exam for the healthy and at-risk neonate that has been used in studies of intrauterine exposure to cocaine [36,41], opiates [11,33], and nicotine [35]. The NNNS follows a relatively invariant sequence of administration that starts with a pre-examination observation, followed by the neurological and behavioral components. The Stress/Abstinence scale is based on signs observed throughout the examination. The NNNS items are summarized into the following scales: Habituation, Attention, Arousal, Regulation, Handling, Quality of Movement, Excitability, Lethargy, Nonoptimal Reflexes, Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence. The sequence of administration and the strategies used by the examiner to maintain an infant’s participation (e.g., swaddling) in the examination are recorded. The examination is administered in a quiet room, midway between feedings with the infant initially asleep and covered if possible. The estimated means of the NNNS summary scores for the exposed and comparison groups regardless of biological caretaker status have been previously reported [53,55].

2.4. Statistical analysis

Maternal and infant characteristics were assessed by one-way analysis of variance (ANOVA) or chi-square. Both maternal depression and prenatal MA exposure were dichotomized independent variables (yes/no). The independent effects of MA exposure and maternal depression were assessed using General Linear Modeling (GLM) with and without covariates (dummy coded prenatal alcohol, tobacco, marijuana, and cocaine exposure, Hollingshead SES, maternal weight gain, and 5-minute Apgar). Covariates were selected based on conceptual reasons, published literature, and maternal and newborn characteristics from Tables 1 and 2 that differed between groups [54]. All covariates were significantly different by MA exposure status. The interaction effect of MA exposure and maternal depression was also tested in the model. Significance was accepted at $p < .05$.

3. Results

3.1. Maternal and infant characteristics

Maternal characteristics of the 136 biological mothers are reported in Table 1. Since we matched for race, insurance status, and education level, it was expected we would find no differences between groups. In addition, no differences were observed with number of prenatal visits, maternal height and age, and pre-pregnancy weight. Relative to the comparison group, MA using mothers were more likely to be of a lower social economic status (SES), have higher incidence of depression and experience greater weight gain during pregnancy.

The newborn characteristics are shown in Table 2. No significant differences between the exposed and unexposed infant groups were found in gender, birth weight, length, head circumference, gestational age, age at time of NNNS administration, and one minute Apgar score. MA exposed infants were more likely to have a lower five minute Apgar score than the unexposed infants.

3.2. Other prenatal drug exposure

The incidence and type of prenatal drug exposure other than MA are reported in Table 3. Since cocaine exposure was an exclusion criteria for the comparison group, there were no infants in the comparison group with cocaine exposure vs. 8 (16.0%) infants in the MA exposed group. MA exposed infants were more likely to be exposed to tobacco, alcohol, and marijuana.

3.3. MA exposure status and maternal depression effects on NNNS

Table 4 shows the NNNS summary scores of the neonates by MA exposure status and maternal depressive symptoms. Missing data occurred when infants did not achieve the state necessary to administer the item, resulting in fewer subjects for habituation, attention, regulation, and handling scales. In the univariate analyses, MA exposure was associated with lower arousal scores ($p=.045$) and higher excitability ($p=.049$). When adjusting for covariates, MA exposure was associated with lower arousal ($p=.014$), and increased lethargy ($p=.008$).

Estimated means of the NNNS summary scores by maternal depression are also shown on Table 4. There were 40 subjects in the maternal depression group and 96 subjects in the non-depressed group. Missing data due to improper state in the infant resulted in slightly reduced samples for attention, regulation, habituation, and handling subscales in both groups. Univariate analyses showed that regardless of exposure status, maternal depression was associated with lower arousal scores ($p=.025$), lower handling (.024), increased hypotonicity ($p=.014$) and increased physiological stress ($p=.003$). When adjusting for covariates, maternal depression was associated with lower arousal ($p=.016$), lower handling (.014), increased hypotonicity ($p=.010$), and increased physiological stress ($p=.002$).

No significant MA exposure by depression interaction was found (Table 4). Thus, prenatal MA exposure combined with maternal depression was not associated with any additional neurodevelopmental differences.

4. Discussion

In western societies, the prevalence of depressive symptomatology during pregnancy has been found to be as high as 25% [9,12,23,26-28,56]. Hormonal changes associated with the reproductive cycle, especially those accompanied by pregnancy, can increase the vulnerability for the onset or recurrence of depression [6]. Women who are diagnosed with depression at approximately one month postpartum are more likely to have been depressed during pregnancy [12,26,48,49], especially in substance abusing women [44].

In the current study, depressive symptoms were more prevalent in the MA using mothers than the controls. This observation is consistent with previous findings that MA using adults tend to have a higher incidence of depression and depressive symptoms than non MA using adults [39,60]. MA use alters neurotransmitters in the brain that are associated with mood and emotional states [16]. Prolonged use of MA has been found to cause damage to the neurotransmitter receptors and presynaptic reuptake mechanisms, and are theorized to be associated with persistent depressive symptoms [50,59].

Despite a significant difference in the incidence of depression in our MA using mothers, the control mothers also had a high incidence of depression. In our sample, 23% of our control mothers experienced prenatal depression where the incidence is typically reported at approximately 10% [17,26]. One explanation is that our control mothers scored high on the Hollingshead Social Position Index which is correlated with a low SES. Numerous investigations have reported that low SES is associated with depression [32]. A second explanation is that both maternal groups had a high rate of smoking. It has been found that smoking is correlated with a 70% increase in the risk of depression in pregnant women [34].

Because smoking is linked with maternal depressive symptoms [34], the high level of depression in the control groups could also be explained by the high incidence of smoking.

Prenatal depression has been found to have numerous effects on neonatal developmental outcomes [22,23,56]. Women with depression often exhibit less positive affect, have lower activity levels [20], and lower quality of maternal care [45,46]. We also found maternal depressive symptoms associated with differences in neonatal neurodevelopment. The scores indicate that neonates with mothers who were depressed during pregnancy had lower excitement levels and muscle tone as compared to infants whose mothers were not depressed. Though difficult to arouse, infants of depressed mothers had more difficulty returning to a normal state. These findings suggest maternal depressive symptoms influence neonatal neurodevelopment.

The influence of prepartum depression on the developing fetus and neonate has been studied previously. Fetuses of women with prepartum depression have elevated heart rates, lower activity levels, less developed motor behavior, an increase in physiological reactivity, and decreased fetal growth [14,15,18,22,23,29,56]. Neonates of women with prenatal depression exhibited inferior performance on the Brazelton's orienting, depression and robustness scales, exhibited more stressed behavior relative to controls, and less facial and vocal expressions than those of non-depressed mothers [1,19,23,56]. Field and colleagues found that during the neonatal period, stress hormones such as norepinephrine and cortisol were significantly elevated in both the depressed mothers and their infants. An increase in neonatal cortisol levels has been found to interfere with the developing child's cognitive skills by making him/her more reactive to stressful situations, less able to focus, and less able to perform complex cognitive tasks [56]. These differences have been attributed to prenatal exposure to a maternal biochemical imbalance [18]. Our findings correspond with Field's findings that maternal depressive symptoms during pregnancy impact neurodevelopment in their offspring as early as the neonatal period.

Contrary to our hypothesis, we did not find differences in the neurobehavior of neonates of depressed MA using mothers relative to non-depressed MA using mothers. Similarly, Singer and colleagues found there were no additional significant differences with cocaine exposure on infant outcome and maternal psychological distress. Maternal psychological distress was characterized by poor motivation, anxiety, and depression [51]. The relationship of prenatal cocaine exposure and maternal depression on neonatal neurodevelopment at one month of age has also been evaluated [49]. The newborns of non-cocaine using depressed mothers demonstrated poorer self-regulation and more stress signs, increased excitability, and increased arousal than those of newborns of cocaine using depressed mothers. The prenatal cocaine exposure seemed to suppress the effects of maternal depression on the newborn.

There are several limitations to the current investigation; therefore these preliminary results should be interpreted with caution. First, we did not assess the mother's depression level at the neonatal visit. In order to accommodate the mothers need for rest during the postpartum period and to accommodate for the limited amount of time the mother is available in the hospital (as few as 24 h), a majority of the questionnaires were designated for the one month visit when a rapport was built between the caretakers and interviewers. Since we included only biological mothers, our sample size was limited to those infants who remained in the custody of their biological mothers at the one month visit. Several of our MA exposed infants were placed in foster care or the care of relatives so the data from their biological mothers was not assessed.

In summary, we found that maternal depression can influence neonatal neurodevelopment. These findings demonstrate the need for additional support services for mothers with depression. Since differences in neurodevelopment can be seen as early as the neonatal period,

support is needed at the first sign of maternal depressive symptoms such as negative affect, a noticeable change in sleeping patterns, or lack of motivation. Early identification of maternal depression and timely intervention may lead to better parenting styles after birth and healthier infant development over time.

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Table 1

Maternal characteristics by MA exposure status

	Mean (SD)/number (percent)		<i>p</i> -value
	Exposed (<i>N</i> =50)	Unexposed (<i>N</i> =86)	
Race			.792
White	27 (54.0%)	36 (41.9%)	
Hispanic	9 (18.0%)	17 (19.8%)	
Pacific Islander	6 (12.0%)	10 (11.6%)	
Asian	4 (8.0%)	13 (15.1%)	
Black	3 (6.0%)	7 (8.1%)	
American Indian	1 (2.0%)	2 (2.3%)	
Other	0 (.0%)	1 (1.2%)	
Public insurance	41 (82%)	73 (84.9%)	.597
# of prenatal visits	12.96 (6.66)	13.73 (4.40)	.422
Education < 12 years	22 (44.0%)	34 (40.0%)	.649
Low SES, Hollingshead-V	15 (30.0%)	9 (10.5%)	.004
SES Hollingshead Social Position Index	25.49 (9.04)	31.51 (10.97)	.001
Depression	20 (40%)	20 (23.3%)	.039
Pre-pregnancy weight (lb)	147.14 (34.38)	139.92 (33.24)	.235
Weight gain (lb)	50.20 (18.53)	35.65 (15.28)	<.001
Height (ft)	5.38 (.24)	5.33 (.21)	.210
Age (year)	25.74 (5.64)	23.99 (5.95)	.094

Table 2

Newborn characteristics by MA exposure status

	Mean (SD)/number (percent)		<i>p</i> -value
	Exposed (<i>N</i> =50)	Unexposed (<i>N</i> =86)	
Gender			.850
Boy	27 (54.0%)	45 (52.3%)	
Girl	23 (46.0%)	41 (47.7%)	
Birth weight (g)	3241.50 (605.04)	3265.73 (587.13)	.819
Length (cm)	50.02 (3.41)	50.92 (3.20)	.126
Head circumference	33.98 (1.77)	33.94 (1.82)	.906
Gestational age	38.94 (1.81)	38.91 (2.07)	.925
Apgar 1	7.60 (1.62)	8.01 (.96)	.065
Apgar 5	8.80 (.70)	8.97 (.24)	.048
Age in days	2.00 (1.64)	2.11 (1.67)	.733

Table 3

Prenatal drug exposure

Substance	Number (percent)		<i>p</i> -value
	Exposed (<i>N</i> =50)	Comparison (<i>N</i> =86)	
Cocaine	8 (16.0%)	Exclusion	—
Tobacco	36 (72.0%)	22 (25.6%)	<.001
Alcohol	24 (48.0%)	14 (16.3%)	<.001
Marijuana	21 (42.0%)	6 (7.0%)	<.001

Table 4

NNNS scale by MA exposure status and maternal depression^a

Measure	Prenatal meth exposure					Maternal depression ^b				
	Yes		No		p=	Yes		No		p=
	N	Mean±S.E.	N	Mean±S.E.		N	Mean±S.E.	N	Mean±S.E.	
Attention	38	5.00 (.17)	72	4.92 (.14)	.719	32	4.92 (.19)	78	5.00 (.13)	.730
Arousal	50	3.93 (.09)	86	4.15 (.07)	.045	40	3.91 (.10)	96	4.17 (.07)	.025
Regulation	48	5.48 (.12)	84	5.29 (.10)	.204	39	5.42 (.13)	93	5.35 (.09)	.683
Handling	39	.29 (.04)	74	.29 (.03)	.903	32	.23 (.05)	81	.35 (.03)	.024
Quality of movement	50	4.43 (.08)	86	4.38 (.07)	.653	40	4.30 (.09)	96	4.50 (.06)	.083
Excitability	50	3.03 (.28)	86	3.73 (.23)	.049	40	3.30 (.31)	96	3.45 (.21)	.685
Lethargy	50	4.82 (.36)	86	4.42 (.31)	.394	40	4.80 (.40)	96	4.44 (.27)	.167
Non-optimal reflexes	50	3.56 (.30)	86	3.27 (.25)	.445	40	3.50 (.33)	96	3.33 (.23)	.663
Asymmetrical reflexes	50	.27 (.09)	86	.32 (.07)	.632	40	.33 (.10)	96	.26 (.07)	.584
Hypertonicity	50	.04 (.02)	86	.11 (.02)	.287	40	.03 (.02)	96	.03 (.02)	.996
Hypotonicity	50	.19 (.05)	86	.22 (.06)	.694	40	.30 (.06)	96	.11 (.04)	.014
Stress/abstinence	50	.12 (.01)	86	.11 (.07)	.293	40	.12 (.01)	96	.12 (.07)	.773
Physiological	50	.04 (.01)	86	.02 (.01)	.272	40	.05 (.01)	96	.00 (.01)	.002
Autonomic	50	.12 (.02)	86	.10 (.02)	.356	40	.09 (.02)	96	.12 (.01)	.256
CNS	50	.15 (.01)	86	.15 (.01)	.799	40	.15 (.01)	96	.15 (.01)	.997
Gastrointestinal	50	.09 (.03)	86	.08 (.02)	.801	40	.10 (.03)	96	.07 (.02)	.611
Visual	50	.12 (.01)	86	.12 (.01)	.783	40	.13 (.02)	96	.12 (.01)	.584
Skin	50	.10 (.02)	86	.09 (.02)	.788	40	.10 (.02)	96	.10 (.02)	.860
State	50	.14 (.02)	86	.11 (.02)	.253	40	.13 (.03)	96	.13 (.02)	.769

^aNo significant MA × Depression interaction on any NNNs variable.

^bMaternal depression was defined by subjects who demonstrated either of the following: a reported lifetime depression+reported serious depression more than two weeks in the last 30 days. OR reported lifetime depression+at least one symptom over the last 30 days.