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Effects of Maternal Breathing Rate, Psychiatric Status, and Cortisol on Fetal Heart Rate

ABSTRACT: *Women's experiences during pregnancy are predictive of variation in neurobehavioral profiles in their children. Few studies have assessed these relationships during the prenatal period. In 113 women in the 36th –38th gestational week (mean age 26.3 ± 5.4 years), electrocardiogram, blood pressure, respiration, salivary cortisol, and fetal heart rate (HR) were measured during baseline, a psychological challenge (Stroop color–word matching task), and a standardized paced breathing protocol. Subjects underwent the Structured Clinical Interview for DSM-IV prior to testing and were grouped as: depressed, co–morbid for depression and anxiety, anxiety disorder only, and control. There was a significant main effect of maternal diagnostic group on fetal HR only during the Stroop task: fetuses of women in the co–morbid group had a greater HR increase compared to controls ($p < .05$). Overall, fetuses showed robust increases in HR during paced breathing ($p < .0001$), and there was no significant difference by maternal diagnosis. For both tasks, changes in fetal HR were independent of women's concurrent cardiorespiratory activity. Finally, although cortisol was higher in the co-morbid group ($p < .05$), across all participants, there was a trend for maternal baseline cortisol to be positively associated with average fetal HR ($p = .06$). These findings indicate that variation in fetal HR reactivity—an index of emerging regulatory capacities—is likely influenced by multiple acute and chronic factors associated with women's psychobiology.* © *2010 Wiley Periodicals, Inc.* Dev Psychobiol

Keywords: *fetal heart rate; cortisol; prenatal depression; fetal heart rate reactivity; paced breathing*

INTRODUCTION

The tremendous plasticity, and activity-dependency of the developing nervous system during fetal life, make this period a prime target for investigations of influences on the course of psychobiological development. Recent research across diverse disciplines has focused on identifying early life origins of adult disease (Godfrey & Barker, 2001), and has demonstrated that factors in pregnant women's health, such as elevations in life stress, may explain some of the individual differences in children's future risk for physical as well as psychological disorders (Barker, 2000; Davis et al., 2004; O'Connor et al., 2005; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Talge, Neal, & Glover, 2007; Van den Bergh & Marcoen, 2004; Van den Bergh et al., 2005).

In our ongoing work, we have reasoned that if the psychosocial functioning of pregnant women affects offsprings' long-term development, we should be able to identify markers of that influence when it occurs, that is, during the prenatal period. In prior reports, we showed that prenatal maternal depression, as well as high-trait

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Abbreviations: HR, heart rate; BP, blood pressure; ANS, autonomic nervous system; CRH, corticotropin releasing hormone; SCID, Structured Clinical Interview for DSM-IV; CES-D, Center for Epidemiological Studies—Depression Scale; HF-HRV, high-frequency heart rate variability.

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anxiety, predict an increase in fetal heart rate (HR) during women's laboratory-based, acute stress experience (Stroop test) compared to fetuses of euthymic women who show no significant HR change (Monk et al., 2000, 2004). Others have found that maternal depression during pregnancy is associated with greater fetal movement and slower return to baseline HR following vibroaccoustic stimulation applied to the women's abdomen (Allister, Lester, Carr, & Liu, 2001; Dieter, Emory, Johnson, & Raynor, 2008). Because increases in fetal HR often are coincident with fetal movements (DiPietro et al., 2004), these findings are consistent in suggesting that greater fetal reactivity to external stimuli may be a characteristic of fetal neurodevelopment when pregnant women experience significant mood dysregulation.

Several studies have attempted to identify characteristics of pregnant women's physiology that are potentially mood-based, and related to alterations in fetal neurobehavior, which would support the concept of women's psychosocial functioning being ''transduced to the fetus'' and shaping fetal development. The maternal HPA-axis has been a focus of this research (Wadhwa, 2005; Weinstock, 2005), as it is a major effector of psychosocial stress, and anxiety and depression are associated with variation in salivary cortisol levels (Heaney, Phillips, & Carroll, 2010; O'Donovan et al., 2010; Veen et al., 2010), even during pregnancy (Evans, Myers, & Monk, 2008). Using a laboratory stressor paradigm similar to ours, Fink et al. (2010) found that fetuses of women who had a cortisol increase following an arithmetic task versus those who did not, had higher resting HR and less short-term HR variability (HRV) 20 min after the stressor task ended. There was a trend finding for participants who had a cortisol increase to report higher levels of life stress (Fink et al., 2010). In other research, higher resting maternal cortisol during the 3rd trimester was associated with greater amplitude and amount (time spent) of fetal movement during a 50-min observation period (DiPietro, Kivlighan, Costigan, & Laudenslager, 2009). Sandman, Wadhwa, Chicz-DeMet, Porto, and Garite (1999) found that higher levels of placenta-derived corticotropin releasing hormone (pCRH; which, in contrast to CRH in the hypothalamus, shows increased synthesis in response to glucocorticoid exposure), predicted increased fetal HR reactivity (''arousal'') studied in a vibroaccoustic habituation paradigm. Taken together, these findings raise the following question for our studies: are differences in fetal HR reactivity associated with maternal psychiatric status influenced by maternal cortisol levels?

So far, we have found minimal indication that women's cardiorespiratory activity during our laboratory protocol was being ''transduced'' to the fetus and determining fetal HR. In response to the stressor, pregnant women showed significant increases in cardiorespiratory activity, and there were no psychiatric group differences in women's responses as there was in fetal HR reactivity (Monk et al., 2000, 2004). Across all subjects, there was only a small inverse association between changes in women's systolic blood pressure (BP) and fetal HR (Monk et al., 2004). Based on these findings, we posited that women's cardiorespiratory reactivity during the stressor task functioned as a stimulus that triggered a HR increase in fetuses of depressed or anxious women *who already had been shaped over the course of gestation* to be more reactive (Monk et al., 2004), possibly via women's HPA-axis activity. To support this interpretation, we sought in this study to manipulate an acute change in maternal cardiorespiratory activity, and investigate it as a possible stimulus for producing changes in fetal HR, which might differentiate fetal reactivity of psychiatrically ill women from nonreactive fetuses. Further, this would be done while simultaneously considering whether maternal cortisol level is associated with fetal HR. Similar to others, we reasoned that a correlation between maternal cortisol and fetal HR in the laboratory likely reflects maternal–fetal experiences outside the laboratory; finding an association would support the hypothesis that over the course of gestation, women's psychosocial functioning shapes fetal development, in part, via maternal HPA-axis activity.

Specifically, the purpose of the present study was to replicate our prior results using the Stroop task and showing a fetal HR increase associated with women's diagnosis of clinical depression (Monk et al., 2004) largely independent of women's HR, BP, and respiration rate changes, and to determine whether women's cortisol is associated with fetal HR. We also used a paced breathing task, in which participants increase and decrease their respiration rate according to a standardized protocol (Wilhelm, Grossman, & Coyle, 2004), to (1) manipulate a specific aspect of women's physiological activity (rapid changes in breathing) to determine its effects on fetal HR and, (2) as a stimulus that can reveal differences in fetal HR reactivity related to women's psychiatric status. Because changes in respiration affect HR (respiratory sinus arrhythmia, which is partially mediated by the vagus nerve), we considered women's cardiac vagal modulation (as indexed by high-frequency HRV, HF-HRV), along with women's HR, BP, and respiration rate activity, in relation to fetal HR.

METHODS

Subjects

Two hundred one women (ages 18–40) in the late 3rd trimester (weeks 36–38), carrying singleton fetuses were recruited from clinics affiliated with Columbia University Medical Center

between July 2001 and March 2006. Women were excluded from entering the study if they smoked during pregnancy, were taking any medications, or if there were any maternal or fetal medical complications such as hypertension, diabetes mellitus, or suspected fetal growth restriction. Forty-six women were dropped from the study for the following reasons: failure to attend sessions, delivery prior to fetal testing session, fetal anomaly, fetal demise, and other serious health problems. Because earlier birth is potentially indicative of a medically compromised intrauterine period, women who gave birth before 37 weeks gestation ($n = 8$) were excluded from all analyses, as were women whose babies' gestational age could not be confirmed from electronic medical records ($n = 28$). Four subjects were removed from analyses because poor quality maternal respiratory signals produced implausible values (4 *SD* below the mean) and two subjects were removed from analyses because maternal diastolic BP was 3 *SD* above the mean. For the remaining sample ($n = 113$), analyses were based on data for variable numbers of data points due to equipment failure, poor quality of fetal data collection, and inadequate saliva sample to determine cortisol concentration. The smallest *n* for any given variable was 105. (Considered across tasks and variables, the range of missing data for subjects by diagnostic group was as follows: 0–3 for anxiety only, 0 for depressed, 0–1 for comorbid, and 0–4 for controls.)

The sample was made up of 60% Latina women, 19% Caucasian, 10% African American, 5% Asian, and 6% of another or mixed ethnicity. Women's age was 26.3 ± 5.4 years ($M \pm SD$). With respect to education, 71.87% of the sample had completed either high school or 2–4 years of college and 18.75% had received an advanced degree. Forty percent of the women were married and 37% of the unmarried were cohabitating. This study was approved by the New York State Psychiatric Institute Institutional Review Board. All subjects gave written, informed consent.

Average gestational age at birth was 39 weeks ($SD = 1$ week, range 37–43 weeks). The average weight at birth was 3,405 g ($SD = 433$, range: 1,984–4,440 g). Fifty-seven percent of the babies were male.

Procedure

During the 2nd trimester, subjects completed demographic questionnaires and were interviewed by a licensed mental health practitioner using the Scheduled Clinical Interview for DSM-IV (SCID) for Axis I disorders (First, Spitzer, Gibbon, & Williams, 1997).

At approximately 36 weeks gestation ($35.9 \pm .8$ weeks), subjects participated in a psychophysiology session. Most sessions were scheduled to begin between 10:30 and 11:30 AM to control for diurnal variations in salivary cortisol levels (though due to scheduling difficulties, some sessions were begun after 12 noon; we controlled for this variation in our analyses). Women completed self-report questionnaires and took part in two laboratory tasks. Subjects were told that they would be asked to rest quietly and then to participate in a "challenging color-word matching task" on the computer (computerized version of the Stroop task) as well as a paced breathing task. Women were instrumented for electrocardiogram, respiration, and BP collection. An ultrasound transducer was placed on the subject's abdomen to record fetal HR. Maternal cardiorespiratory and fetal HR data were obtained during five periods: while the subjects rested quietly for a 5-min baseline, during the 5-min Stroop color-word matching task, during a first 5-min recovery period, during the 6-min paced breathing task, and during a second 5-min recovery period (Fig. 1). Participants rated the periods with respect to stress they experienced on a 1–10 scale. Also salivary cortisol was collected at three time points: (1st) after the subject arrived and consent was obtained, (2nd) just before the psychophysiology recording session started, but after a brief practice of the forthcoming tasks, and (3rd) just after the psychophysiology recording session ended (Fig. 1). There was approximately 25–30 min between each sample. To obtain assays of cortisol, subjects were instructed to suck and chew on a cotton roll for 1 min or until saturated.

The Stroop Task. The Stroop task presents subjects with color words in either congruently or incongruently colored letters and asks the subject to identify the color of the letters. It is commonly used to induce stress in a laboratory setting (Renaud & Blondin, 1997) or as a cognitive assessment of executive function (Bugg, Jacoby, & Toth, 2008). In our version, the subject was required to push keys that corresponded to the correct color responses as fast as possible. If responses were incorrect or too slow, the computer displayed the message "incorrect" on the screen. To augment the cognitive performance demands, the experimenter prompted subjects to work faster throughout the task.

Paced Breathing. This task requires subjects to control their breathing by inhaling when a bar on a computer screen rises and to exhale when it falls (Wilhelm et al., 2004). During the task, subjects alternate among periods of breathing at a faster than

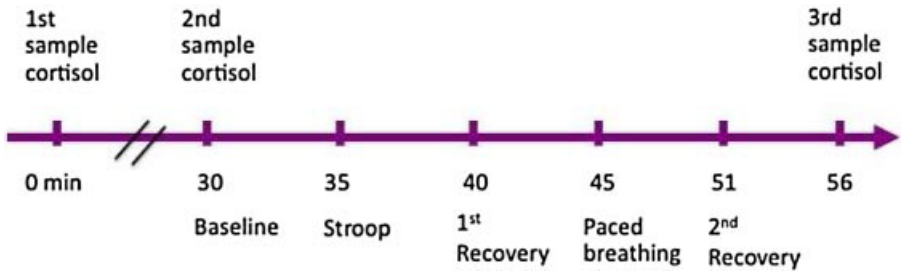

FIGURE 1 Laboratory protocol.

normal rate (approximately 30 bpm), a slower than normal rate (about 10 bpm), and at an approximately normal rate (20 bpm). As paced by the computer, the breathing rates change every 30 sec.

Stress Ratings for Study Periods. Participants were asked to rate the stress they experienced on a 1 (not at all) to 10 (extreme stress) scale after each of the periods of the experiment, except for the 2nd recovery.

Salivary Cortisol. Saturated cotton rolls enclosed in sealed tubes were stored at −20°C until time of assay. Saliva extracted from these cotton rolls was analyzed at the Analytical Psychopharmacology Laboratories at the Nathan Kline Institute. Cortisol was measured by radioimmunoassay using primary antibodies and I^{125} labeled cortisol purchased from ICN Biomedicals, Irvine, CA. The cortisol standards used were from Sigma Chemical Co., St. Louis, MO. Samples were assayed in duplicate. The intra- and inter-assay coefficients of variation were 3.0% and 6.0% at the 3.1 μg/dl level.

Acquisition and Processing of Maternal and Fetal Signals. Maternal electrocardiogram and respiration impedance signals from a Hewlett Packard 78292A monitor were digitized at 500 and 50 samples/sec, respectively, using a 16-bit A/D card (National Instruments, Austin, TX, 16XE50). Software written by LEDONA Solutions, Inc., New York, NY, was used to mark R-waves and create files of RR-intervals (RRI). R-wave markings were visually inspected and corrected where necessary. Mean HR was computed for all subjects. Spectral power in the high (.15–.50 Hz) frequency band was computed as recommended by the Task Force Report on Heart Rate Variability (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Spectra were calculated on 300-sec epochs using an interval method for computing Fourier transforms similar to that described by Deboer, Karemaker, and Strackee (Deboer, Karemaker, & Strackee, 1984). Prior to computing Fourier transforms, the mean of the RRI series was subtracted from each value in the series and the residual series was then filtered using a Hanning window (Harris, 1978) and the power, that is, variance over the HF band was summed. Estimates of spectral power were adjusted to account for attenuation produced by this filter (Harris, 1978). Peaks in the impedance respiratory waveform also were marked. These marks were verified by visual inspection and then were used to calculate respiratory rate. BP was acquired on a beat-to-beat basis by an Ohmeda Finapres 2300 monitor. The analog pressure waveform was digitized at 250 Hz. Systolic BP and diastolic BP values were marked by peak/trough detection software and errors in marking were corrected interactively. Fetal HR was recorded via an ultrasound transducer (Advanced Medical Systems, Littleton, CO, IM76) and digitized at 50 Hz (for details, Monk et al., 2004).

Women's Psychiatric Status. Based on results from the SCID interview conducted in the 2nd trimester, women with a current major depressive disorder and/or dysthymia were classified as depressed ($n = 7$). None of the depressed women had bipolar disorder. Women who currently had a social phobia, a simple phobia, generalized anxiety disorder, or agoraphobia without panic disorder were classified as having an anxiety disorder only ($n = 25$). Women with depression and an anxiety disorder, including post-traumatic stress disorder, were classified as comorbid ($n = 13$). Women free of Axis I pathology were classified as controls ($n = 68$). There were no diagnostic group differences in the distribution of women's ethnicity and/or race.

Self-Report of Depression. Current symptoms of depression were measured at the time of the fetal study using the Center for Epidemiological Studies—Depression Scale (CES-D). The CES-D is a 20-item questionnaire with a possible score range from 0 to 60. A score of 16 or more is considered an indication of depression. The validation and use of the CES-D in community samples has been well established (Boyd, Weissman, Thompson, & Myers, 1982; Radloff, 1977; Roberts, 1980).

Data Analyses

Analytic Plan. Mean values for fetal HR and women's HR, HF-HRV, BP, and respiration rate were computed for each of the discrete periods (baseline, Stroop, 1st recovery, paced breathing, and 2nd recovery). Fetal HR during the Stroop and paced-breathing tasks was modeled using separate linear mixed models with random intercepts. All analyses were carried out using SAS 9.1.3 PROC MIXED procedure. Women's diagnostic group, study period (i.e., baseline, Stroop, 1st recovery, paced breathing, 2nd recovery) and their interactions were the primary predictors in both models. Although we collected cortisol at three time points during the laboratory session (Fig. 1) with the aim of considering change in cortisol in relation to change in fetal HR, there were no differences in cortisol over time (all $ps > .10$, a finding that is consistent with some data on HPA-axis activity in pregnant women (Evans et al., 2008; Kammerer, Adams, Castelberg, & Glover, 2002; Slattery & Neumann, 2008), though not all (de Weerth, Wied, Jansen, & Buitelaar, 2007; Fink et al., 2010). In analyses, the 2nd cortisol sample, acquired before the psychophysiology session started, but after a period of acclimation to the laboratory, was used to index maternal cortisol level. Maternal cortisol level, time of cortisol collection (morning vs. after 12 noon), fetal sex, and gestational age at time of testing were included in the models because they were either a primary variable of interest (cortisol, time of cortisol collection) or other studies supported their relevance to the outcome variables (sex; Buss et al., 2009; Weinberg, Sliwowska, Lan, & Hellemans, 2008), or their addition corrected for possible bias related to nonrandom group assignment (sex, gestational age). Other potential covariates were additively introduced into the original models and the resulting −2 restricted log-likelihood values were obtained. The difference between the −2 restricted log-likelihood values for the original and the current model was used to approximate the chi-squared distribution with degrees of freedom equal to the difference in parameters estimated. The covariate was kept in the model if the deviance analysis yielded a statistically significant result and also that it was clinically and statistically significant. Interactions were tested using the same techniques discussed above. However, interactions were kept in the model only

Table 1. List of Covariates Tested for Model Building

Model	Variable Description[a]
1	Original model[b]
2	Ethnicity
3	Education
4	Maternal age
5	Birth weight
6	Number of children
7	HR
8	Systolic BP
9	Diastolic BP
10	Respiratory rate
11	HF-HRV
12	Stress ratings
13	CES-D score[c]

[a]Each covariate, from adjacent and concurrent study period, as well as change from prior period, was added to the original model and tested for goodness-of-fit.

[b]Original model covariates include the following: test time effects, diagnostic group effects, interaction of test time and diagnostic group effects, fetal sex, gestational age, cortisol sample time, and cortisol levels.

[c]Self-report of depression at time of laboratory session, which could vary from time of initial diagnosis.

if the parameter estimates yielded significant results. Table 1 presents lists of covariates that were tested to obtain the final working model (HF-HRV values were log transformed to correct for skewness.) None of the proposed covariates were maintained in the final models because they did not significantly alter the results (*p*-values for effects on model deviances all $>.10$). With regard to maternal diagnosis, the control group was the reference category. With regard to effects of period, for the first model, the baseline was the reference period while for the second model, the period immediately prior to paced breathing (i.e., the 1st recovery period) was the reference period.

The magnitude of maternal cardiorespiratory reactivity during the Stroop and paced breathing periods was computed as a within-subject change (e.g., average value during Stroop− average value during baseline). Changes in stress ratings from prior rest periods to the following task were computed similarly. ANOVAs were used to make comparisons of diagnostic group differences in women's physiological activity, stress ratings to the tasks, and cortisol levels; Student's *t*-tests were used to characterize the significance of the physiologic reactivity and change in stress level.

RESULTS

Women's Cardiorespiratory Activity: Baseline and Stroop

Women's cardiorespiratory activity during baseline and the Stroop task is summarized in Table 2. ANOVAs

Table 2. Maternal Cardiorespiratory Activity and Fetal HR During Baseline, Stroop, and, Paced Breathing Periods

	Baseline (±*SD*)	Stroop (±*SD*)	1st Recovery (±*SD*)	Paced Breathing (±*SD*)	2nd Recovery (±*SD*)	Change from Baseline to Stroop (±*SD*)[a]	Change from 1st Recovery to Paced Breathing (±*SD*)[a]
HR (bpm)	89.4[b] (±13.3)	91.7 (±12.3)	89.1[b] (±11.6)	90.0 (±12.5)	87.6 (±12.8)	2.3 (±6.5)****	.9 (±4.8)
Systolic BP (mmHg)	111.1 (±14.0)	119.8 (±16.1)	113.7 (±14.7)	111.1 (±16.1)	116.6 (±15.2)	8.7 (±9.0)****	−2.6 (±7.3)****
Diastolic BP (mmHg)	64.1 (±9.9)	68.9 (±10.8)	65.3 (±10.5)	64.1 (±11.2)	68.2 (±13)	4.8 (±6.0)****	−1.2 (±5.4)**
Respiration (bpm)	19.8 (±5.0)	24.1 (±5.5)	20.1 (±5.1)	21.1 (±4.9)	18.3 (±6.6)	4.0 (±7.2)****	1.0 (±5.2)*
HF-HRV (log-transformed values)	5.2 (±1.5)	4.7 (±1.3)	5.4 (±1.3)	5.8 (±1.3)	5.4 (±1.4)	−.5 (±.8)***	.4 (±.9)***
Stress rating (scale 1–10)	2.1 (±1.8)	4.8 (±2.2)	2.2 (±1.7)	3.6 (±2.2)	N/A	2.7 (±2.2)****	1.4 (±2.1)****
Fetal HR (bpm)	146.7 (±9.1)	147.3 (±8.9)	146.4 (±9.6)	150.4 (±9.7)	151.5 (±10.6)	.6 (± 5.5)	4.0 (±7.2)****

N/A, not applicable; stress rating not determined following the 2nd recovery period.

[a]Paired *t*-tests were used to evaluate significance of reactivity (baseline to Stroop and 1st recovery to paced breathing.

[b]ANOVAs revealed no diagnostic group differences in maternal HR, BP, and respiration rate during any of the four periods (baseline, Stroop, 1st recovery, paced breathing) except for maternal HR during baseline and 1st recovery ($ps < .05$); post hoc analyses indicated women in the anxiety only group compared to controls had higher HR during baseline (96.6 bpm vs. 86.7 bpm, LSD, $p = .002$) and during the 1st recovery (95.1 bpm vs. 86.7; LSD, $p = .004$).

$^{*}p < .05$.
$^{**}p < .01$.
$^{***}p < .001$.
$^{****}p < .0001$.

revealed no diagnostic group differences in maternal HR, BP, HF-HRV, and respiration rate during baseline or Stroop except for maternal HR during baseline ($p < .05$); post hoc analyses indicated that women in the anxiety disorders group differed from controls; they had higher HR during baseline (96.6 bpm vs. 86.7 bpm, LSD, $p = .002$). There were also no diagnostic group differences in the changes in women's cardiorespiratory reactivity to the Stroop task (all $ps > .30$). (There was a trend finding $p = .06$ for women in the anxiety group to have a smaller decrease in HF-HRV from baseline to the Stroop task.) In the absence of significant diagnostic group differences, women's cardiorespiratory reactivity during the Stroop period was analyzed across all subjects using single-sample *t*-tests. On average, women showed significant HR, BP, HF-HRV, and respiration rate changes to the Stroop task compared to baseline values (all $ps < .05$; Tab. 2).

Women's Self-Reports of Stress: Baseline and Stroop

There were no significant diagnostic group differences in women's stress ratings during the baseline or Stroop periods ($p = .08$ and .22, respectively), and groups did not differ in the increase from baseline to the Stroop task ($p = .7$). As can be seen in Table 2, women on average reported experiencing a significant increase in stress from the baseline to the Stroop period (all $ps < .0001$).

Women's Cardiorespiratory Activity: 1st Recovery and Paced Breathing

Similar to the findings for the Stroop challenge, ANOVAS revealed that except for maternal HR during 1st Recovery, there were no diagnostic group differences in the women's cardiorespiratory activity values for the 1st recovery or paced breathing periods (all $ps > .5$; Tab. 2). For the 1st recovery, post hoc analyses (least squares differences, LSD) indicated women in the anxiety only group compared to controls had higher HR (95.1 bpm vs. 86.7; $p = .004$). There were also no diagnostic group differences in the changes in women's cardiorespiratory reactivity to the paced breathing task (all $ps > .11$). In the absence of diagnostic group differences, women's cardiorespiratory reactivity during the paced breathing period was analyzed across all subjects using one-sample *t*-tests. On average, women showed significant BP, respiration rate, and HF-HRV changes to the paced breathing task compared to values during the prior recovery period (1st recovery, $ps < .05$), but there was no significant change in HR.

Women's Self-Reports of Stress: 1st Recovery and Paced Breathing

There were no significant diagnostic group differences in women's stress ratings during the 1st recovery or paced breathing periods ($p = .06$ and .8, respectively), and groups did not differ in the increase from the 1st recovery to the paced breathing task ($p = .5$). As can be seen in Table 2, women on average reported experiencing a significant increase in stress from the 1st recovery to the paced breathing period ($p > .001$).

Women's Cortisol Levels

Table 3 reports women's cortisol levels by diagnostic group as an ANOVA showed significant group difference in women's resting cortisol level (F (3, 101) = 2.72, $p = .05$); post hoc analysis indicated that women in the comorbid group had significantly higher cortisol levels compared to controls ($p = .01$). (When time of cortisol collection was controlled for, AM vs. PM, the results remained the same.)

Modeling Fetal Heart Rate: Stroop and Adjacent Resting Periods

A linear model with random intercept showed that across all subjects, fetal HR did not change during the Stroop task; however, there was an interaction effect of diagnostic group and period such that fetuses of women in the comorbid group (i.e., depression and an anxiety disorder) had a significantly larger increase in HR during the Stroop task compared to controls ($p < .05$; Tab. 4

Table 3. Women's Cortisol Levels by Diagnostic Group

	Anxiety Disorders Only ($n = 17$)	Comorbid ($n = 12$)	Depression ($n = 7$)	Control ($n = 61$)
Cortisol (ng/ml)	1.9 ± 3.2	2.8 ± 3.2^a	$.8 \pm 1.3$	1.1 ± 1.5

[a]There was a significant group difference in cortisol levels (F (3, 101) = 2.72, $p = .05$); post hoc analysis indicated that women in the comorbid group had significantly higher cortisol levels compared to controls (LSD, $p = .01$).

Table 4. Linear Mixed Model With Random Intercept: Fetal HR During Stroop and Adjacent Baseline and Recovery Periods

Variables	Estimate (β)	Standard Error	p-Value
Group effects			
Comorbid versus controls	−1.0	3.2	.8
Depressed versus controls	−5.1	3.3	.1
Anxiety disorders versus controls	−3.2	2.3	.2
Time effects			
Baseline to 1st recovery	−.7	.8	.4
Baseline to Stroop	−.7	.8	.4
Time × group effects			
Baseline to 1st recovery: comorbid versus controls	−1.8	2.1	.4
Baseline to 1st recovery: depressed versus controls	1.5	2.3	.5
Baseline to 1st recovery: anxiety versus controls	.3	1.7	.9
Baseline to Stroop: comorbid versus controls	4.9	2.1	**.02**
Baseline to Stroop: depressed versus controls	2.7	2.4	.3
Baseline to Stroop: anxiety versus controls	2.3	1.7	.2
Covariates			
Sex (male = 0, female = 1)	−1.9	1.6	.2
Gestational age	−.4	1.1	.7
Cortisol sample time (AM = 0, PM = 1)	−1.8	2.0	.3
Cortisol level	1.1	.6	**.06**

Reference group effects = controls. Reference time period = baseline. Bold indicates significant, or near significant effects.

and Fig. 2). In this model, there was also a trend for maternal cortisol to be positively associated with fetal HR ($p = .06$), such that, across all subjects, greater maternal cortisol at baseline was associated with overall higher fetal HR across all periods. There were no significant main effects of diagnostic group on fetal HR at resting baseline or during the recovery period following the Stroop task, or other interaction effects with diagnostic group and period. (Other possible variables (described in the methods section, that is, maternal cardiorespiratory activity) were not included in the model due to non-significance.)

Modeling Fetal Heart Rate: Paced Breathing and Adjacent Resting Periods

A linear model with random intercept showed that fetal HR significantly increased during the paced breathing

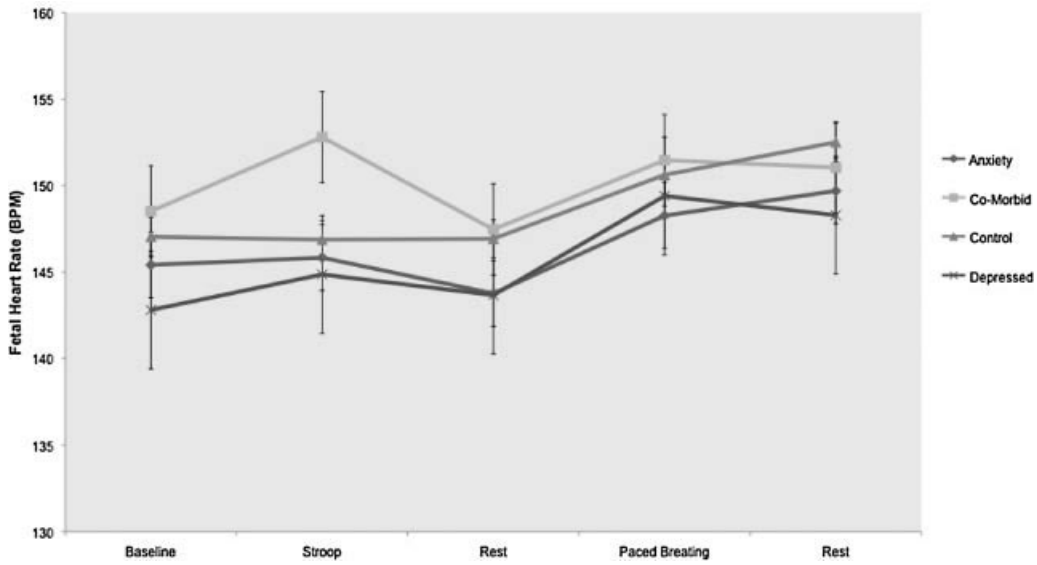

FIGURE 2 Fetal HR during laboratory protocol by women's diagnostic status.

task ($p < .0001$) and during the subsequent recovery period ($p < .001$) relative to the resting period before the breathing task (Tab. 5 and Fig. 2). There was no significant interaction between diagnostic groups and these changes in fetal HR. No other variables were significant.

However, during paced breathing, women were asked to alter their breathing rate a total of five times over the course of the task. An average of women's respiration rate or HR over the entire period may mask acute changes associated with fetal HR. Thus, in addition to associations between 5-min averages of maternal cardiorespiratory and fetal HR examined in the model, we considered associations between maternal cardiorespiratory and fetal HR during each of the 1-min intervals of paced breathing. An examination of maternal HR, systolic BP, diastolic BP, and respiration rate with fetal HR for each minute of paced breathing revealed only one significant correlation (out of 20 possible): during minute 4 of paced breathing there was a positive association between women's respiration rate and fetal HR ($r = .28$, $p < .01$).

Stroop Versus Paced Breathing: Comparing Maternal Cardiorespiratory Reactivity

The fetal HR response during maternal exposure to the Stroop versus paced breathing tasks differed (i.e., only fetuses of comorbid women showed a response to the Stroop task, while, on average, all fetuses showed a HR increase during paced breathing), yet women's contemporaneously collected cardiorespiratory activity, including HF-HRV, was not associated with fetal HR during these periods (Methods for model description and Tabs. 4 and 5). To consider if variation in the magnitude in women's cardiorespiratory reactivity between the tasks functioned as divergent stimuli to the fetuses such that greater maternal cardiorespiratory activity during paced breathing could account for the robust fetal HR increase during this period, we compared maternal reactivity between Stroop and paced breathing. Student's *t*-tests comparing women's cardiorespiratory reactivity indicated that maternal HR, BP, and respiration rate responses were greater during Stroop compared to paced breathing (and in the opposite directions for BP; increased during Stroop and decreased during paced breathing; all ps $< .05$, Tab. 2).

However, as indicated, during paced breathing, women were asked to increase and decrease their breathing rate frequently so that the period average respiration rate change from 1st recovery to paced breathing does not reflect the magnitude of these multiple changes in breathing rate during this period. To better characterize the magnitude and frequency of maternal respiration rate changes for the paced breathing task, and compare the results to similarly derived results for the Stroop task, we calculated minute-by-prior minute changes in respiration rate (e.g., average breathing rate during the 2nd minute of the task compared to the 1st, etc.) for both periods. Women's average minute-by-prior minute changes in respiration rate were 6–9 times larger during paced breathing than the spontaneous changes occurring during the Stroop task (all *t*-tests all $p < .0001$).

Table 5. Linear Mixed Model With Random Intercept: Fetal HR During Paced Breathing and Adjacent Rest Periods

Variables	Estimate (β)	Standard Error	*p*-Value
Group effects			
Comorbid versus controls	−.8	3.7	.8
Depressed versus controls	−2.8	4.0	.5
Anxiety disorders versus controls	−3.0	2.8	.3
Time effects			
1st recovery to 2nd recovery	6.1	1.1	**.0001**
1st recovery to paced breathing	4.2	1.1	**.0001**
Time × group effects			
1st recovery to 2nd recovery: comorbid versus controls	−.9	3.0	.7
1st recovery to 2nd recovery: depressed versus controls	−1.5	3.2	.6
1st recovery to 2nd recovery: anxiety versus controls	−.4	2.3	.9
1st recovery to paced breathing: comorbid versus controls	1.1	2.8	.7
1st recovery to paced breathing: depressed versus controls	1.5	3.2	.6
1st recovery to paced breathing: anxiety versus controls	.6	2.3	.8
Covariates			
Sex (male = 0, female = 1)	−2.2	1.9	.2
Gestational age	1.3	1.3	.3
Cortisol sample time (AM = 0, PM = 1)	−.7	2.1	.7
Cortisol level	.6	.7	.4

Reference group effects = controls. Reference time period = 1st recovery. Bold indicates significant, or near significant effects.

DISCUSSION

In this study of 3rd trimester pregnant women undergoing a psychophysiology protocol consisting of two laboratory tasks, there were no diagnostic group differences in women's cardiorespiratory reactivity to the tasks based on their psychiatric classification, though there was a trend result for women in the anxiety only group to show a smaller decrease in HF-HRV. Except for HR during baseline and the 1st recovery period, when women with anxiety disorders had a higher HR than controls, there were no other differences in cardiorespiratory activity in these rest periods. In contrast, pregnant women comorbid for depression and anxiety had higher cortisol than women with depression only, an anxiety disorder, or who were controls.

There were also diagnostic group differences in fetal HR reactivity to the Stroop task. Fetuses of women comorbid for depression and an anxiety disorder showed a greater HR increase during women's exposure to the Stroop task compared to fetuses of women with only depression, an anxiety disorder, or no psychiatric illness. There were no diagnostic group differences in fetal HR responses to the paced breathing task, when, on average, all subjects showed a significant HR increase.

In modeling fetal HR, none of the maternal cardiorespiratory variables from the baseline or task periods was retained, as they did not reach significance. However, there was a trend for women with higher levels of salivary cortisol to have fetuses with higher HR during the Stroop task and the two adjacent rest periods ($p < .06$). Cortisol failed to reach statistical significance in the model of fetal HR for paced breathing and the associated rest periods.

Fetal HR activity during the Stroop task, distinguished by a HR increase unique to fetuses of women comorbid for depression and anxiety, is consistent with our hypothesis and prior results (though see below for a discussion of the discrepancy in results regarding which psychiatric condition shows the effect). In the absence of correlations between contemporaneously collected maternal and fetal cardiorespiratory activity, and in the context of similar maternal cardiorespiratory reactivity to the Stroop task across diagnostic groups, the data suggest the possibility that fetuses of women with comorbid depression and anxiety are more reactive to stimuli than those of women with only an anxiety disorder, depression only, or euthymic mood.

The marginally significant positive association between maternal cortisol and fetal HR does not clearly support or challenge the hypothesis that mood-based alterations in women's HPA-axis activity may affect the fetus, and influence fetal neurobehavioral development over the course of gestation. Glucocorticoid exposure affects synaptogenesis, neurotransmitter function, and glucocorticoid receptor expression in the developing brain (Owen, Andrews, & Matthews, 2005), with far-reaching implications for neurobehavioral development. DiPietro's studies showing that (1) fetal HR and movement are often coincident (DiPietro et al., 2004; DiPietro, Hodgson, Costigan, & Johnson, 1996a), (2) that higher maternal cortisol is associated with greater fetal movement (DiPietro et al., 2009), and (3) that there is continuity between fetal neurobehavior and infant temperament (DiPietro et al., 2002; DiPietro, Hodgson, Costigan, & Johnson, 1996b) suggest the possibility that the fetal HR/maternal cortisol association seen here may be a proxy for a fetal movement/maternal cortisol relationship—an interpretation in line with the effects of cortisol on the developing nervous system and studies showing a positive association between women's prenatal cortisol levels and more reactive infant temperament (Davis et al., 2007; de Weerth, van Hees, & Buitelaar, 2003). In future studies, we plan to collect data on fetal movement.

Alternatively, our marginal cortisol result is somewhat in line with Fink et al., who found higher HR in fetuses of women who had an acute cortisol increase to a laboratory stressor (Fink et al., 2010). Animal studies indicate that prenatal exposure to glucocorticoids is associated with increased cardiac growth (Rudolph, Roman, & Gournay, 1999), as well as enhanced vascular sensitivity to the vasoconstrictive actions of the hormone angiotensin II, which may contribute to a developmental increase in peripheral resistance and cardiac output (Frasch et al., 2007; Tangalakis, Lumbers, Moritz, Towstoless, & Wintour, 1992). It has been hypothesized that glucocorticoids inhibit the release of vasodilatory prostaglandins, which typically function to blunt the vasoconstrictive actions of angiotensin II (Tangalakis et al., 1992). In the short-term, acute increases in glucocorticoids enhance the sympathetically mediated cardiovascular responses to stimuli, such as a HR increase (Sapolsky, Romero, & Munck, 2000; Sorrells & Sapolsky, 2007). One study with human infants showed that fetal exposure to exogenous synthetic glucocorticoids (betamethasone) for anticipated preterm birth predicts greater HR reactivity to a heel stick blood draw at 34 weeks postconceptual age (Davis et al., 2006). Higher fetal HR during women's laboratory stress experience may be influenced by chronic and/or acute elevations in women's cortisol, though a recent report on the mediating role of women's anxiety on the function of a placental enzyme that renders cortisol largely inactive (11βHSD2) (Glover, Bergman, Sarkar, & O'Connor, 2009) suggest that future research must consider the activity of this enzyme in studies on the prenatal influences of women's psychosocial functioning and HPA-axis activity.

Contrary to our hypothesis, there was no main effect of diagnostic group on fetal HR during the paced breathing

task; fetuses of women in all groups demonstrated similar marked increases in HR during the paced breathing task. Furthermore, maternal cortisol levels were not associated with fetal HR during paced breathing and the associated rest periods, nor was maternal cardiorespiratory activity, including HF-HRV. In the absence of associations between maternal and fetal physiology, at least as tested here, it seems possible that the changes in women's respiratory activity during paced breathing, which were far greater than during the Stroop task, functioned as a suprathreshold in utero sensory stimulus to the fetus, and thereby elicited equivalent robust increases in fetal HR across all groups. Rapid changes in women's respiration may activate multiple fetal senses, including auditory, proprioceptive, and vestibular. When the stimuli are multimodal, frequent, and of great magnitude (i.e., during paced breathing), fetuses in all groups respond. A recent study using a similar paced breathing paradigm with pregnant women showed that that there was an increase in the number of ''synchronized epochs'' between maternal and fetal HRs when women's respiration rate was faster (i.e., 20 bpm) compared to her average rate. In part, the authors interpreted the results as showing that the fetus can adjust its cardiac rate in response to external (maternal) stimuli (Van Leeuwen et al., 2009). Alternatively, because the tasks were not counterbalanced, it may be that fetal exposure to a second maternal task (and associated changes in the intrauterine environment) is of sufficient duration to affect most fetuses and elicit a HR increase.

The findings from the paced breathing task are consistent with other data showing that fetuses respond to stimuli (Lecanuet & Schaal, 1996; Novak, 2004; Sandman et al., 1999), and are in agreement with results from a recent report by DiPietro, Costigan, Nelson, Gurewitsch, and Laudenslager (2008), who showed that fetal motor activity is suppressed and HRV augmented in response to divergent maternal tasks (relaxation and stressful cognitive challenge) and associated opposing maternal HR and skin conductance reactivity. DiPietro et al. (2008) interpret their data as indicating that the fetal responses are the result of fetal perception of changes in the intrauterine environment associated with the protocol manipulations, and thus reflective of a fetal orienting response to sensory stimulation.

Our results showing that fetuses from the group of women comorbid for depression and anxiety showed greater fetal HR response during women's exposure to the Stroop task varies from our prior results in which fetus of depressed women showed this effect (Monk et al., 2004). The small number of subjects in both studies in the depressed and comorbid groups, and the associated increased influence of outliers, could account for the discrepancies between the prior and current findings. In the 2004 sample, for fetuses of women in the depressed group, the average fetal HR change to Stroop was 3.2 ± 1.1 bpm; in the current sample, 3.8 ± 6.5 bpm and 2.1 ± 3.1 bpm, for the depressed and comorbid groups, respectively, indicating greater variability in the current results (all are unadjusted values).

It is also possible that these results are similar to other nonspecific findings in psychiatry in which risk factors and biological markers (here, fetal HR) are associated with more than one category of DSM-IV psychiatric illness, particularly when the diagnostic categories share clinical features and are often comorbid, as is the case with depression and anxiety (Gottesman & Hanson, 2005; Kendler, 2005; Rommelse, Van der Stigchel, & Sergeant, 2008). Future investigations are needed to further explore the reliability of the original finding with respect to maternal depression, and to replicate our current results.[1]

Similar to our prior study (Monk et al., 2004), in this work, fetuses of women with only anxiety disorders did not show a HR response during women's exposure to the Stroop task. This finding continues to be unexpected, and warrants further exploration, in particular, an examination of undetected acute effects. The higher HR during baseline for women in the anxiety group, as well as the trend finding of a smaller decrease in their HF-HRV from the baseline to the Stroop period, may indicate that pregnant women with anxiety disorders have a different cardiorespiratory profile which influences fetal HR activity.

On the other hand, the adjusted values for fetal HR change from the baseline to the Stroop period (Tab. 4) show that fetuses of women in each diagnostic group have a greater HR increase than fetuses of control women, though the results are only statistically significant for those of comorbid women. As an exploratory post hoc analysis, we modeled fetal HR for the Stroop and adjacent periods using only two maternal groups, positive for a psychiatric diagnosis versus euthymic controls, and the same covariates as in Table 4. There was a significant effect for diagnostic group ($p < .05$), such that fetuses of women with a psychiatric illness had a 3.1 bpm increase in

[1]Although it was not an aim of this study to investigate associations between the level of self-reported anxiety in control women and fetal HR reactivity, we note that unlike our prior results, there was no such relationship in these data. Again, we find a possible reason to be inconsistency in diagnosing between the studies. Fifteen percent were classified in the anxiety disorder group in the 2004 study (Monk et al., 2004), whereas in this sample, the proportion is 22%. We hypothesize that the greater identification of women as belonging in the anxiety disorder group in the recent sample reduced the number of women scoring high on trait anxiety in the control group—some of whose fetuses might have shown a HR increase to the Stroop task. This hypothesis is supported by a comparison of fetal HR change in the anxiety disorder groups between the two studies: In the 2004 sample, the average fetal HR change during the Stroop task for those in the anxiety disorder group was $-.03 \pm .8$ bpm versus $+.65 \pm 5.2$ bmp in this current sample.

HR during the Stroop period compared to those of controls; higher cortisol was associated with higher fetal HR ($p < .05$).

SUMMARY

When women were exposed to the Stroop task, fetuses of women with comorbid depression and anxiety had a HR increase, independent of women's cardiorespiratory reactivity. Contrary to our hypothesis, women's cortisol levels showed only a trend association with fetal HR. Though the pathway remains unspecified, the results are consistent with the hypothesis that prolonged exposure to physiological factors associated with women's mood dysregulation throughout pregnancy alters fetal neurobehavioral development, resulting in greater reactivity to some environmental perturbations in affected fetuses. During paced breathing, externally driven rapid and dramatic increases in women's respiration rate was associated with acute changes in fetal HR regardless of diagnostic group status and independent of associations with women's contemporaneously collected cardiorespiratory activity, indicating a fetal HR response to in utero stimulation. Emerging processes of neurobiological regulation, as well as individual variation in these developing capacities, can be identified in the prenatal period.

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