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Fetal heart rate variability mediates prenatal depression effects on neonatal neurobehavioral maturity

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ABSTRACT

This study analyzed the mediating role of fetal heart rate variability (FHR) on prenatal depression and neonatal neurobehavioral maturity. A sample of 104 pregnant women was recruited and divided into two groups according to their Edinburgh Postnatal Depression Scale (EPDS) scores (depressed/non-depressed). FHR variability in response to speech stimuli was assessed at term (between 37 and 39 weeks gestation). The neonates were then assessed on the Neonatal Behavioral Assessment Scale (NBAS) during the first 5 days after birth. The fetuses of non-depressed pregnant women showed higher HR variability than the fetuses of depressed pregnant women in response to speech stimuli, and later as neonates they performed more optimally on the NBAS (on autonomic stability and total scores). FHR variability mediated the relationship between the mother's prenatal depression and the neonateís NBAS performance. Prenatal depression effects on neonatal behavior may be partially explained by its adverse effects on fetal neurobehavioral maturity.

Prenatal depression (assessed in any of the three different trimesters) has been associated with both delayed fetal growth and delayed neonatal growth, but in separate studies. Delayed fetal growth has included lower fetal head circumference, length and weight (e.g., Conde et al., 2010; Diego et al., 2009; Henrichs et al., 2010), and delayed neonatal growth has included preterm birth and low birth-weight (e.g., Grote et al., 2010; Neggers, Goldenberg, Cliver, & Hauth, 2006; Straub, Adams, Kim, & Silver, 2012). Prenatal depression has also been associated with both delayed fetal neurobehavioral maturity and delayed neonatal neurobehavioral maturity, but again in separate studies. Prenatal depression (during the second or the third trimester) effects on delayed fetal neurobehavioral maturity have included greater fetal activity (e.g., Dieter, Emory, Johnson, & Raynor, 2008) and higher fetal heart rate (FHR) (e.g., Allister, Lester, Carr, & Liu, 2001; Monk et al., 2011; Monk et al., 2004). A slower FHR reactivity and a delay in return to baseline after vibroacoustic stimulation (Allister et al., 2001) has also been reported in one study, while a greater FHR reactivity to a lab-induced stressor was reported in another study on depressed mothers during the third pregnancy trimester (Monk et al., 2011; Monk et al., 2004).

Delayed neonatal neurobehavioral maturity following prenatal depression during the third trimester has been evidenced by lower vagal tone and delayed HR deceleration, and by less optimal neurobehavioral and socio-emotional performance (e.g., Davis et al., 2004; Figueiredo, Pacheco, Costa, Conde, & Teixeira, 2010; Jones, 2012; Pacheco & Figueiredo, 2012; Zuckerman, Bauchner, Parker, & Cabral, 1990). For example, in a face/voice preference paradigm neonates of prenatally depressed women during the third trimester did not show a visual/auditory preference for the mother's face/voice, required more trials for habituation to the mother's face/voice, and showed a greater visual/auditory preference for the stranger's face/voice after habituation compared to neonates of prenatally non-depressed women (Figueiredo et al., 2010; Pacheco & Figueiredo, 2012). Newborns of depressed mothers during the third trimester had lower basal parasympathetic tone and responded with less vocal distress, but were delayed in physiological regulation following the cry of another infant (Jones, 2012). In another study,

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maternal anxiety and depression at the third trimester, but not at 4 months postpartum, were related to infant negative behavioral reactivity to novelty at 4 months (Davis et al., 2004).

On the Brazelton Neonatal Behavioral Assessment Scale (NBAS), neonates of prenatally depressed mothers (at the second or third pregnancy trimester) showed less optimal performance on habituation, orientation, motor, range of state, autonomic stability, and depression scales (Field et al., 2004), on habituation, regulation of state, and range of state (Pacheco & Figueiredo, 2012), and on the orienting to face/voice stimulus, alertness, cuddliness, and hand-to-mouth activity items (Hernandez-Reif, Field, Diego, & Ruddock, 2006). Male newborns of prenatally depressed mothers at the third pregnancy trimester had lower scores than controls on the NBAS motor skills and regulation of states clusters in another study (Gerardin et al., 2011).

Negative effects of prenatal depression on fetal and neonatal growth were not demonstrated in other studies (e.g., Bödecs et al., 2011; Maina et al., 2008; Suri et al., 2007; Wisner et al., 2013). In these studies, prenatal depression was assessed during all different trimesters of pregnancy – at the first trimester (e.g., Bödecs et al., 2011; Suri et al., 2007), at the second trimester (e.g., Maina et al., 2008; Suri et al., 2007; Wisner et al., 2013), or at the third trimester (e.g., Suri et al., 2007; Wisner et al., 2013). Interestingly, all these studies reporting no impact of prenatal depression on fetal or neonatal outcomes included only growth measures (for example, weight, length and head circumference), and have not assess fetal and infant neurobehavioral maturity. These inconsistent findings highlight the need for further studies covering both the fetal and the neonatal periods and focusing on fetal outcomes more vulnerable to the effect of women's prenatal depression and more related with later infant developmental dimensions. However, maternal pregnancy-psychological stress has been associated with accelerated neurobehavioral maturation in at least one study (DiPietro et al., 2010). These inconsistent findings highlight the need to discriminate between the effect of maternal normative and non-normative psychological symptoms during pregnancy on the neonate neurobehavioral maturity.

We hypothesized that prenatal depression's effect on FHR variability could be an underlying mechanism leading to the poorer developmental outcomes of infants born to prenatally depressed women. Reduced FHR variability has been associated with other detrimental conditions, including women's prenatal stress and low SES (e.g., DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996; DiPietro, Costigan, Shupe, Pressman, & Johnson, 1998). Low FHR variability has been a marker of delayed fetal neurobehavioral maturity (e.g., DiPietro, Costigan, & Voegtline, 2015), and was shown to be a predictor of delayed mental and language development in early childhood (Bornstein et al., 2002; DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). However, literature lacks on longitudinal studies that analyzed the developmental trajectories of infants born to prenatally depressed women measuring FHR variability. Additionally, differences on FHR responses to various stimuli, including speech stimuli, have been providing support for the prenatal capacity to differentiate among stimulus proprieties (e.g., DiPietro et al., 2015). However, as much as we know the effect of prenatal depression on FHR variability in response to speech stimuli was not investigated.

The present study analyzed the mediating role of FHR variability on the relationship between prenatal depression and neonatal neurobehavioral maturity. FHR variability may reflect emerging individual differences in the development of the autonomic and central nervous systems related to later neurobehavioral maturity (e.g., Appelhans & Luecken, 2006; DiPietro et al., 2007, 2015). The effect of prenatal depression on FHR variability in response to speech stimuli was also analyzed.

2. Methods

2.1. Participants

All *primigravid* pregnant women attending routine prenatal care for low-risk pregnancy were contacted in two primary health care centers in the North of Portugal. Only those who were able to read, write, and speak Portuguese were approached during the second trimester of pregnancy, and 88.6% agreed to participate. Given that less favorable socio-demographic conditions are associated with prenatal depression and less optimal neonatal development (Orr & Miller, 1995), group (depressed vs. non-depressed) equivalence on socio-demographics was ensured. A sample of 104 pregnant women was selected according to their depression scores: 52 were depressed (EPDS ≥ 9) and 52 were non-depressed (EPDS < 9). Random stratified sampling was used to ensure (depressed and non-depressed) group equivalence on maternal age ($\leq$29 vs. >30 years), years of schooling (<9 vs. ≥ 9 years of schooling), professional status (employed vs. unemployed), and matrimonial status (married or cohabiting vs. single). All mothers were Caucasian, primiparous and Portuguese. Most of them were less than 30 years old, had nine or less years of schooling, were employed, and married or cohabiting. The fetuses were singleton and considered at low-risk. Most of them were born at term, were of normal weight and length, and had an Apgar score equal or higher than 7 (see Table 1).

No associations were noted between the depressed and non-depressed groups on pregnancy and delivery medical data, including gestational age, $\chi^2(1) = 0.44$, $p = 0.741$, type of delivery, $\chi^2(2) = 3.89$, $p = 0.143$, epidural anesthesia, $\chi^2(1) = 0.94$, $p = 0.332$, resuscitation at birth, $\chi^2(1) = 0.08$, $p = 1.000$. Further, the groups did not differ on neonatal measures, including one minute Apgar score, $\chi^2(1) = 0.39$, $p = 0.534$, weight, $\chi^2(1) = 0.17$, $p = 0.680$, length, $\chi^2(1) = 0.27$, $p = 0.601$), head circumference, $\chi^2(1) = 1.44$, $p = 0.231$, and gender, $\chi^2(1) = 0.04$, $p = 0.843$; see Table 1).

Some women failed to attend the scheduled fetal EKG monitoring session ($n = 19$, 18.3%; $n = 6$ depressed, $n = 13$ non-depressed, $\chi^2(1) = 2.32$, $p = 0.128$), because of premature birth ($n = 9$; $n = 3$ depressed, $n = 6$ non-depressed), failure to follow the guidelines for daily reading of the nursery rhymes between 33 and 37 weeks ($n = 3$ depressed), transfer to another medical institution ($n = 3$ depressed), or other reasons ($n = 4$; $n = 1$ depressed, $n = 3$ non-depressed). No associations were found between women who failed to attend the fetal EKG monitoring session and those who attended the fetal EKG monitoring session on maternal age, $\chi^2(1) = 0.54$, $p = 0.331$, years of schooling, $\chi^2(1) = 0.89$, $p = 0.261$, professional status, $\chi^2(1) = 0.14$, $p = 0.469$, matrimonial status, $\chi^2(1) = 1.06$, $p = 0.381$, and depression, $\chi^2(1) = 0.10$, $p = 0.487$, on pregnancy and delivery medical data, including gestational age, $\chi^2(1) = 0.40$, $p = 0.529$, type of delivery, $\chi^2(1) = 2.75$, $p = 0.098$, epidural anesthesia, $\chi^2(1) = 0.69$, $p = 0.792$, resuscitation at birth, $\chi^2(1) = 0.32$, $p = 0.573$, and on neonatal measures, including one minute Apgar score, $\chi^2(1) = 0.46$, $p = 0.497$, weight, $\chi^2(1) = 3.65$, $p = 0.060$, length, $\chi^2(1) = 3.14$, $p = 0.080$, head circumference, $\chi^2(1) = 2.29$, $p = 0.130$, and gender, $\chi^2(1) = 0.83$, $p = 0.362$.

2.2. Procedures

2.2.1. Prenatal period (3rd trimester)

This study was approved by the institution's Ethics Committee and had the voluntary participation of the pregnant women who signed an informed consent. Pregnant women were interviewed to collect socio-demographic data the EPDS (between 28 and 33 weeks gestation, $M = 32.06$, $SD = 3.34$). They were instructed to recite a short nursery rhyme out loud to their fetuses every day three times successively, between the 33rd and the 37th week ges-

Table 1
Mother's socio-demographics, pregnancy and delivery medical data and neonatal measures.

			Total (N = 104) (%)		
Mother	Age (years)[a]	≤29	57.7		
		>30	43.3		
	Years of schooling[a]	<9	55.6		
		≥9	44.4		
	Professional status[a]	Employed	69.2		
		Unemployed	30.8		
	Matrimonial status[a]	Married/cohabiting	92.3		
		Single	7.7		
			Total (N = 104) (%)	Non-depressed (n = 52) (%)	Depressed (n = 52) (%)
Pregnancy and delivery	Gestational age	<37	9.6	38	5.8
		≥37	90.4	46.2	44.2
	Type of delivery	Vaginal	75.0	42.0	33.0
		Caesarean	25.0	9.0	16.0
	Epidural anesthesia	No	13.0	5.0	8.0
		Yes	87.0	46.0	41.0
	Resuscitation at birth	No	91.0	46.0	45.0
		Yes	9.0	5.0	4.0
Neonate	Apgar index: 1st min	<7	3.1	1.0	2.0
		≥7	96.9	50.0	46.9
	Weight (g)	<2500	5.0	3.0	2.0
		≥2500	95.0	48.0	47.0
	Length (cm)	<48	18.8	8.4	10.4
		≥48	81.2	41.6	39.6
	Head circumference	<33	10.4	7.3	3.1
	(cm)	≥33	89.6	44.8	44.8
	Gender	Male	56.7	27.9	28.8
		Female	43.3	22.1	21.2

[a] Random stratified sampling criteria.

tation. A total of 49.5% were randomly assigned to rhyme "A", and 50.5% to rhyme "B". A researcher (AP) contacted each mother one or two times during this period, to ensure that the procedure was being conducted correctly.

A routine EKG examination was performed at term (between 37 and 39 weeks gestation, M = 37.48, SD = 0.60) to evaluate FHR response to speech stimuli, while pregnant women wore headphones for classical music that was being played to mask maternal perception of the presented stimuli. A female researcher (AP) recorded both nursery rhymes and presented them during the examination after a 5-min period of low fetal reactivity – 1F state or stable baseline with absent or only sporadic and short-lasting accelerations: 0 or 1 acceleration <30 s and <20 beats per minute; long-term variability ≤ 10 bpm in 50% of the segment or less (pretest phase). The rhymes were presented with a loudspeaker (Sony CFD-6) at 82 dB, held approximately 20 cm above the women's abdomen. Each nursery rhyme was played for 15 s and was repeated in the order "ABABBA" (55.2%) or "BABAAB" (48.9%), for a total of 90 s. An additional 15 s were recorded with no stimulus being presented (posttest phase).

FHR were recorded continuously and stored using the Omniview-SisPorto system (Ayres-de-Campos, Sousa, Costa, & Bernardes, 2008). A Hewlett Packard M1351 fetal monitor (currently commercialized by Philips Healthcare, Amsterdam, the Netherlands) was used to export FHR signals every 0.25 s in beats per minute, rounded to the nearest quarter of a beat. Data were subsequently exported to an Excel 2007 worksheet, to be analyzed in the eight different 15-s intervals.

2.2.2. Neonatal period

On the first five days after birth (1 to 5 days, M = 2.66, SD = 1.67) the NBAS (Brazelton & Nugent, 1995) was performed. Newborn's age (hours of life) did not differ, $t(98) = -1.08$, $p = 0.283$, across the two groups. The examination was conducted by a trained and reliable examiner (AP) midway between feedings in a quiet and semi-darkened room with a temperature of 22°–27 °C. The NBAS was scored immediately after it was performed.

2.3. Measures

2.3.1. Prenatal depression

The Edinburgh Postnatal Depression Scale (EPDS, Cox, Holden, & Sagovsky, 1987) is a self-report questionnaire comprised of 10 items on a 4-point Likert scale (0–3) that has been used to assess women's prenatal depression. The EPDS Portuguese version showed good internal consistency (Cronbach's alpha = 0.85). A score equal or greater than 9 indicates the probable presence of a depressive episode during pregnancy (Tendais, Costa, Conde, & Figueiredo, 2014). In the present sample, Cronbach's alpha revealed good internal consistency (Cronbach's alpha = 0.89).

2.3.2. Fetal heart rate (FHR) variability

FHR variability in response to speech stimuli (a familiar and a novel nursery rhyme) was recorded while being given a routine EKG examination. After a 5-min period of stage 1F low fetal activity (pretest phase), each rhyme was repeatedly played for a total of 90 s (6 × 15 s). Thereafter, further 15 s were recorded with no stimulus being presented (posttest phase).FHR variability, the difference between the highest and lowest FHR frequency value, was calculated for the pretest phase, the first presentation of the familiar speech stimulus, the first presentation of the novel speech stimulus and the posttest phase. The total FRH variability was calculated by averaging these values.

2.3.3. Neonatal neurobehavioral maturity

The Neonatal Behavioral Assessment Scale (NBAS, Brazelton & Nugent, 1995) assesses newborn's competencies across different neurobehavioral areas – autonomic, motor, states and social orientation. This scale, comprised of 28 behavioral and 18 reflex items, is suitable for examining newborns and infants up to two months old. The 28 behavior items are scored on a 9-point scale and the 18 reflex items on a 3-point scale. The scores were computed

according to the eight subscales – habituation, orientation, motor, range of state, regulation of state, autonomic stability, excitability, depressed, and a total score (Costa et al., 2010). Higher scores indicate better neonatal neurobehavioral performance (Lester, Als, & Brazelton, 1982). In the present sample, Cronbach's alphas of the subscales ranged from 0.60 to 0.87 and the Cronbach's alpha of the NBAS total score was 0.72.

2.4. Statistical procedure and data analysis

To assess the effect of women's prenatal depression (coded as depressed ≥ 9 vs. non-depressed <9) on FHR variability in response to speech stimuli, a multivariate analysis of variance (MANOVA) and a repeated-measures analysis of variance (ANOVA) were performed. The MANOVA model included women's prenatal depression as the independent variable and FHR variability (pretest, familiar speech stimulus, novel speech stimulus, and posttest) as dependent variables. The repeated-measures ANOVA model included women's prenatal depression as the between-subject factor and FHR variability as the repeated measures factor with four levels: pretest, familiar speech stimulus, novel speech stimulus, and posttest. Pairwise comparisons were applied to assess depressed and non-depressed group differences on FHR variability during the pretest, familiar speech stimulus, novel speech stimulus, and posttest. To assess the effect of women's prenatal depression on total FHR variability an independent sample *t*-test was performed.

To assess the effect of women's prenatal depression (coded as depressed ≥ 9 vs. non-depressed <9) on neonatal neurobehavioral maturity, a MANOVA was performed. The model included women's prenatal depression as independent variable and neonatal neurobehavioral maturity (habituation, orientation, motor, range of state, regulation of state, autonomic stability, excitability, depression) as dependent variables. To assess the effect of women's prenatal depression on NBAS total score, an independent sample *t*-test was performed. Bonferroni corrections were applied in all models.

To analyze the mediating role of FHR variability on the relationship between prenatal depression and neonatal neurobehavioral maturity, four different linear regressions were conducted (forced entry method).

According to recommendations (Baron & Kenny, 1986), the test of the linkages was performed (see Fig. 1). In the first equation, prenatal depression was entered as the independent variable and FHR variability (total) as the criterion (Path a). In the second equation, FHR variability was entered as the independent variable and neonatal neurobehavioral maturity (NBAS total score) as the criterion (Path b). In the third equation, prenatal depression was entered as the independent variable and neonatal neurobehavioral maturity as the criterion (Path c). The fourth equation included prenatal depression and FHR variability as independent variables and neonatal neurobehavioral maturity as the criterion (Path c'). The Sobel test was performed.

Statistical analyses were performed using SPSS version 20 (SPSS Inc., USA). The statistical assumptions regarding the statistical analyses were confirmed. Post hoc power calculations, using the software G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) revealed that the sample size (104 women) was adequate to detect medium-to-large effect sizes on the MANOVAs (effect size f range = 0.23–0.56, $p < 0.05$, n range = 85–104, groups = 2, response variables range = 4–8, power range = 0.94–0.99), and in the repeated measures ANOVA (effect size f range = 0.29–0.59, $p < 0.05$, $n = 85$, correlation of the repeated measures = 0.72, power = 1.0), and small to medium effect sizes in the linear regression analyses (effect size f^2 range = 0.05–0.32, $p < 0.05$, predictors range = 1–2, power range = 0.70–0.99). Effect size measures ($p\eta^2$ and R^2) are presented for all analyses.

All available data were included in the analysis. Women who attended the EKG monitoring session were not different from those who did not on socio-demographic, pregnancy and delivery, and neonatal variables. For this reason, attendance at the EKG monitoring session was not controlled for in the statistical analysis.

No fetus gender differences were found on FHR variability in the pretest, $t(83) = -0.13$, $p = 0.897$, familiar, $t(83) = -0.06$, $p = 0.953$, or novel, $t(83) = -0.05$, $p = 0.959$, speech stimulus, in the posttest, $t(83) = -0.29$, $p = 0.771$, and total FHR variability, $t(83) = -0.19$, $p = 0.853$. Additionally, no gestational age differences were found on FHR variability in the pretest, $t(83) = -0.25$, $p = 0.806$, familiar, $t(83) = -0.60$, $p = 0.550$, or novel, $t(83) = -0.82$, $p = 0.786$, speech stimulus, in the posttest, $t(83) = -0.27$, $p = 0.786$, and total FHR variability, $t(83) = -0.62$, $p = 0.539$. For this reason, these variables were not controlled for in the statistical analysis.

3. Results

3.1. Prenatal depression effect on FHR variability

The MANOVA results were statistically significant, *Wilk's Lambda* = 0.71, $F(4,80) = 8.11$, $p < 0.001$, $p\eta^2 = 0.29$. The univariate analyses revealed statistically significant effects of prenatal depression on FHR variability in response to a familiar stimulus, $F(1,83) = 25.63$, $p < 0.001$, $p\eta^2 = 0.24$. Fetuses of depressed pregnant women had lower HR variability in response to a familiar speech stimulus than fetuses of non-depressed pregnant women (mean difference of 6.74). Additionally, the independent *t*–test revealed a significant effect of prenatal depression on total FHR variability, $t(83) = 2.59$, $p = 0.011$. Fetuses of depressed pregnant women showed lower total HR variability than fetuses of non-depressed pregnant women (mean difference of 2.42).

The repeated-measures ANOVA revealed a significant interaction effect between prenatal depression and FHR variability in response to a familiar and a novel speech stimulus, $F(3,249) = 9.27$, $p < 0.001$, $p\eta^2 = 0.10$. The fetuses of depressed women showed lower FHR variability in response to a familiar speech stimulus than posttest FHR variability, $p = 0.004$ (mean difference of 3.85), whereas the fetuses of non-depressed women showed higher FHR variability in response to a familiar speech stimulus than in response to a novel stimulus, $p = 0.003$ (mean difference of 4.64), pretest, $p = 0.007$ (mean difference of 5.66), and posttest, $p = 0.047$ (mean difference of 2.60; see Table 2).

3.2. Prenatal depression effect on neonatal neurobehavioral maturity

The MANOVA results were statistically significant, *Wilk's Lambda* = 0.83, $F(8,95) = 2.49$, $p = 0.02$, $p\eta^2 = 0.17$. The univariate analyses revealed statistically significant effects of prenatal depression on neonates' autonomic stability, $F(1,102) = 4.51$, $p = 0.03$, $p\eta^2 = 0.05$. Neonates of depressed women had lower scores on autonomic stability than neonates of non-depressed women. Additionally, the independent *t*–test results revealed a significant effect of prenatal depression on the NBAS total score (neurobehavioral maturity), $t(102) = 2.54$, $p = 0.01$. Neonates of depressed pregnant women had lower NBAS total scores than neonates of non-depressed pregnant women (mean difference of 2.09; see Table 3).

3.3. FHR variability mediation effect

The mediation model to test whether FHR variability mediated the relationship between prenatal depression and neonatal neurobehavioral maturity is presented in Table 4 and in Fig. 1.

Table 2
Between and within group differences for HR variability in fetuses of prenatally depressed and non-depressed women.

	Depressed $n = 46$		Non-depressed $n = 39$		
	M	*SD*	*M*	*SD*	*F*(1,83)
FHR variability					
Pretest (a)	7.82	3.88	9.47	7.40	1.74
Familiar stimulus (b)	6.33	3.27	13.06	8.31	25.63***
Novel stimulus (c)	7.41	3.74	8.42	4.94	1.15
Posttest (d)	10.18	6.29	10.46	6.86	0.04
	b < d[1]		b > a, c, d[2]		
			t(83)		
Total FHR variability	7.93	2.54	10.35	5.51	6.61*

[1] Pairwise comparisons applied to depressed women, b < d, $p = 0.004$.
[2] Pairwise comparisons applied to non-depressed women, a < b, $p = 0.007$; b > c, $p = 0.003$; b > d, $p = 0.047$.
* $p < 0.05$.
*** $p < 0.001$.

Table 3
Means (and standard deviations) for NBAS scores in neonates of prenatally depressed women and non-depressed women.

	Depressed $n = 52$		Non-depressed $n = 52$		Univariate	
	M	*SD*	*M*	*SD*	*F*(1,102)	$p\eta^2$
NBAS scores						
Habituation	4.81	3.54	5.63	3.36	1.48	0.01
Orientation	5.42	2.05	5.16	2.10	0.39	0.01
Motor	5.32	0.71	5.57	0.62	3.45	0.03
Range of state	3.94	0.76	4.13	0.56	2.20	0.02
Regulation of state	5.50	1.27	5.89	1.20	2.58	0.03
Autonomic stability	6.13	1.04	6.55	0.87	4.92*	0.05
Excitability score	1.33	1.31	1.04	1.08	1.50	0.01
Depressed score	1.83	2.28	2.38	2.77	1.26	0.01
	t(102)					
NBAS total score	34.27	4.01	36.36	4.34	6.45	–

Notes. *Wilk's Lambda* = 0.867, $F(8,95) = 2.48$, $p = 0.02$, $p\eta^2 = 0.17$.
* $p < 0.05$.

Table 4
Mediation model: FHR variability mediates the relationship between prenatal depression and neonatal neurobehavioral maturity.

Variable	R^2 (R^2Aj)	*F*	β	*p*
a. FHR variability	0.08 (0.06)	6.69*		
Prenatal depression			−0.27	0.011
b. Neonatal neurobehavioral maturity	0.09 (0.08)	8.19**		
FHR variability			0.30	0.005
c. Neonatal neurobehavioral maturity	0.06 (0.05)	6.44*		
Prenatal depression			−0.24	0.013
c'. Neonatal neurobehavioral maturity	0.11 (0.09)	5.16**		
Prenatal depression FHR variability			−0.150.26	0.159 0.020

Sobel test = −2.08, *SE* = 0.40, $p = 0.042$.
* $p < 0.05$.
** $p < 0.01$.

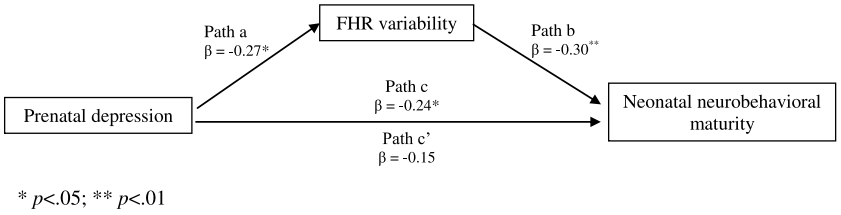

Fig. 1. Mediation model results: FHR variability mediates the relationship between prenatal depression and neonatal neurobehavioral maturity.

The first linear regression (Path a) revealed a statistically significant model that explained 6% of the variance, $F(1,83) = 6.69$, $p = 0.011$, $R^2AJ = 0.06$. Prenatal depression was identified as a predictor of lower FHR variability (total), $\beta = -0.27$, $t = -2.59$, $p = 0.011$.

The second linear regression (Path b) revealed a statistically significant model that explained 8% of the variance, $F(1,83) = 8.19$, $p = 0.005$, $R^2AJ = 0.08$. Lower FHR variability was identified as a predictor of lower neonatal neurobehavioral maturity (lower NBAS total score), $\beta = 0.30$, $t = 2.86$, $p = 0.005$.

The third linear regression (Path c) revealed a statistically significant model that explained 5% of the variance, $F(1,102) = 6.44$, $p = 0.013$, $R^2AJ = 0.05$. Prenatal depression was identified as a pre-

dictor of lower neonatal neurobehavioral maturity, $\beta = -0.24$, $t = -2.54$, $p = 0.013$.

The fourth linear regression model (Path c') was also statistically significant and explained 9% of the variance, $F(2,82) = 5.16$, $p = 0.008$; $R^2AJ = 0.09$. Lower FHR variability was identified as a predictor of lower neonatal neurobehavioral maturity, $\beta = 0.26$, $t = 2.38$, $p = 0.020$. However, prenatal depression was no longer a predictor of lower neonatal neurobehavioral maturity, $\beta = -0.15$, $t = -1.42$, $p = 0.159$. This result reveals the mediating role of FHR variability in the relationship between prenatal depression and neonatal neurobehavioral maturity. Additionally, the Sobel test was statistically significant (*Sobel test* = −2.08, *SE* = 0.40, $p = 0.042$), suggesting the indirect effect of the independent variable (prenatal depression) on the dependent variable (neonatal neurobehavioral maturity), via the mediator (FHR variability).

4. Discussion

Fetuses of prenatally depressed women showed lower HR variability in response to a familiar speech stimulus as well as lower total HR variability than fetuses of prenatally non-depressed women. Fetuses of prenatally depressed women also showed lower HR variability in response to a familiar speech stimulus than to posttest, whereas fetuses of prenatally non-depressed women presented higher HR variability in response to a familiar speech stimulus than in response to a novel stimulus, pretest and posttest. These results suggest lower neurobehavioral maturity in fetuses of prenatally depressed women and are consistent with previous empirical data on lower FHR variability but in fetuses of prenatally stressed mothers (e.g., DiPietro et al., 1996, 1998).

These results suggest lower neurobehavioral maturity in fetuses of prenatally depressed women, since HR variability reflects the rate of the neural maturation of the fetus (DiPietro et al., 2015). HR variability has been conceptually linked to nervous system maturation that results on a balance of parasympathetic and sympathetic innervation (Freeman, Garite, & Nageotte, 1991). Lower HR variability may imply an autonomic nervous system (ANS) dysfunction and a decreased ability of the sinus node of the heart to respond to *external* signals, therefore a reduced ability to adapt to the environment (Lazinski, Shea, & Steiner, 2008). Lower FHR variability is a sign of lower fetal neurobehavioral maturity and suggests a possible sympathoadrenal dysregulation in the fetuses of prenatally depressed women (DeGangi, DiPietro, Greenspan, & Porges, 1991).

HR variability is a psychophysiological process related with an individual capacity for behavioral and autonomic regulation, but is also a response variable (Porges, 2007), "an indicator of attentional status during periods of challenge or effort" (DiPietro et al., 2015, p. 24). FHR variability is a measure of an active form of attention. Changes in FHR variability are measures of mental effort or attention, and are concomitant with changes in the behavioral fetus states from low to high variation during rest and activity periods (Porges, 2007). Fetuses were considered to discriminate between familiar and novel voices, according to their HR increases in the presence of the mother's voice and decreases in the presence of the stranger's voices (Kisilevsky et al., 2003). According, a higher HR variability would be expected in response to a familiar speech stimulus, if recognized. That is what happened with the fetuses of prenatally non-depressed women, but not with the fetuses of prenatally depressed women. Although these results need to be interpreted with caution, they reaffirm the suggested lower fetal neurobehavioral maturity in fetuses of prenatally depressed women as they do not give the signal (high HR variability) that they are responding to a challenging stimulus (as it is recognizing a familiar speech).

Neonates of the prenatally depressed women performed less optimally on the NBAS (lower autonomic stability and total scores) than neonates of prenatally non-depressed women. These results are consistent with other empirical data showing lower NBAS scores in the neonates of prenatally depressed women (e.g., Field et al., 2004; Gerardin et al., 2011; Pacheco & Figueiredo, 2012). Lower NBAS scores are an indication of less neonatal neurobehavioral maturity. Several studies have found a relation between maternal depression and newborn performance on the NBAS (e.g., Abrams, Field, Scafidi, & Prodromidis, 1995; Hernandez-Reif et al., 2006), but few explored specifically the effect of prenatal depression (e.g., Field et al., 2004; Gerardin et al., 2011; Pacheco & Figueiredo, 2012). Neonates of prenatally depressed women performed less optimally specifically on the NBAS, and specifically on the autonomic stability subscale. The autonomic stability NBAS scale reflects signs of stress related to homeostatic adjustments of the central nervous system (Brazelton & Nugent, 1995). The neonatal behavior on this subscale is closely related to the ANS via parasympathetic activation (Costa et al., 2010). Neonates of the prenatally depressed women seem to have less ANS regulation, which is also consistent with their lower FHR variability data, linking specific elements of lower neurobehavioral maturity during the gestational and after the childbirth period.

The results also suggest that the prenatal depression effect on neonatal neurobehavioral maturity is mediated by lower FHR variability. Several studies have shown that prenatal depression is associated with poor neonatal outcomes (e.g., Field et al., 2004; Figueiredo et al., 2010; Jones, 2012). The current study suggests that the impact of the womenís depression on fetal neurobehavioral maturity is a possible explanation for the poorer developmental outcomes of infants born to prenatally depressed women. In the present study, the fetuses of prenatally depressed women showed lower total HR variability, and in turn, lower FHR variability predicted less optimal neonatal neurobehavioral maturity. The relationship between prenatal stress and diminished FHR variability has been reported (e.g, DiPietro et al., 1996, 1998). Further, significant stability of FHR variability has been shown during pregnancy (after 28 weeks gestation) and throughout the first year of life (e.g., DiPietro et al., 2007). And, diminished FHR variability was a predictor of delayed mental and language development in early childhood (Bornstein et al., 2002; DiPietro et al., 2007). However, this is the first study to showing FHR variability as a mediator of the association between prenatal depression and neonatal neurobehavioral maturity. Although the low amount of variance explained by this model highlights the need for exploring additional mediator variables for this association.

An important line of research concerns which fetal measures are the best predictors of abnormal development in early infancy (DiPietro et al., 2007). In this study, FHR variability was shown to mediate the relationship between prenatal depression and neonatal neurobehavioral maturity. Data indicate that the effect of prenatal depression on neonatal neurobehavioral maturity results from the negative effect observed in FHR variability. Autonomic function during gestation seems stable from the fetal to neonatal periods, and appears to predict developmental outcomes (DiPietro et al., 2007). Lower FHR variability seems to be a physiological marker for vulnerability to developmental delay (Monk et al., 2004).

When we examined our data, no differences were noted between the depressed and non-depressed mothers' groups on pregnancy and delivery medical data. Prenatal depression did not seems to affect pregnancy outcomes, in this study in which sociodemographic variables were controlled during group assignment. Other authors found similar results, particularly when examining community samples (e.g., O'Donnell, O'Connor, & Glover, 2009). Non-optimal pregnancy outcomes seem to occur in the less favorable socioeconomic samples (Orr & Miller, 1995).

Some hypotheses have been proposed for possible mechanisms to explain the impact of prenatal depression on fetal neurobehavioral maturity. Barkerís fetal programming hypothesis (Barker, 2004) states "*the environment in utero can alter the development of the fetus . . . with a permanent effect on the phenotype*" (Van den Bergh, Mulder, Mennes, & Glover, 2005, p. 238). For example, womenís elevated cortisol associated with depression can cross the placenta, altering the in utero environment, affecting the fetus and disturbing ongoing developmental processes (maternal-fetal HPA axis deregulation). A second possible underlying process is increased uterine artery resistance and the limited blood flow to the fetus (e.g., O'Donnell et al., 2009). Inadequate prenatal care and less healthy habits associated with depression can also affect fetal neurobehavioral maturity (e.g., Monk, Georgieff, & Osterholm, 2013; Nordentoft et al., 1996; Spann et al., 2015). The limitations of this study include the self-reported prenatal depression. Nonetheless, the EPDS is one of the measures most commonly used and was validated to assess depression during pregnancy and the postpartum period (e.g., Tendais et al., 2014). The randomization was limited to participants' age, years of schooling, and professional and marital status. The authors acknowledge that other variables, that were not identified or controlled for, may have biased the results. For example, the similarity versus the difference between how the mother versus the female researcher recite the rhymes was not tested (Table 4).

Implications for future studies can be noted. It would be interesting to explore which stage of pregnancy depression has its most adverse impact on FHR variability, and if the persistence of depression during pregnancy has a greater impact on FHR variability. Following the sample and repeating the measures would also clarify the impact on later development. The results of the present study are consistent with a previous finding, but on lower FHR variability in fetuses of stressed mothers (e.g., DiPietro et al., 1996, 1998). To better explore fetal processes underlying the specific effect of prenatal depression on neurobehavioral maturity, prenatal anxiety would also need to be controlled, considering that depression and anxiety are comorbid during pregnancy (e.g., Figueiredo & Conde, 2011). The cumulative effects of prenatal depression and anxiety on FHR variability would also need to be explored.

This study shows the negative impact of prenatal depression on fetal and neonatal neurobehavioral maturity. Further, FHR variability was a mediator of the relationship between prenatal depression and less optimal neonatal neurobehavioral maturity. These data are particularly important given that decreased HR variability precedes the development of a number of abnormal conditions (e.g., DiPietro, Costigan, & Gurewitsch, 2003). Conversely, higher HR variability has been linked to the control of attention, emotion, behavior, and cognition (e.g., DeGangi et al., 1991; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), to higher self-regulation, and to more stable and positive moods (e.g., Porges, McCabe, & Yongue, 1982). Further research is needed to clarify the potential long-term effects of prenatal depression on infant development, specifically examining the impact of duration, timing, and severity of the depressive symptoms on different dimensions of infant development and other possible mediators of these effects. FHR variability is a promising measure for accessing fetal neurobehavioral conditions (DiPietro et al., 2015; Porges, 2007).

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