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Maternal depression across the first years of life compromises child psychosocial adjustment; relations to child HPA-axis functioning

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ABSTRACT

Maternal depression across the first years of life negatively impacts children's development. One pathway of vulnerability may involve functioning of the hypothalamic-pituitary-adrenal (HPA) axis. We utilize a community cohort of 1983 women with no comorbid risk repeatedly assessed for depression from birth to six years to form two groups; chronically depressed ($N = 40$) and non-depressed ($N = 91$) women. At six years, mother and child underwent psychiatric diagnosis, child salivary cortisol (CT) was assessed three times during a home-visit, mother-child interaction was videotaped, and child empathy was coded from behavioral paradigms. Latent Growth curve Model using Structural Equation Modeling (SEM) estimated the links between maternal depression and mother's negative parenting and three child outcomes; psychopathology, social withdrawal, and empathy as related to child CT baseline and variability. Depressed mothers displayed more negative parenting and their children showed more Axis-I psychopathology and social withdrawal. SEM analysis revealed that maternal depression was associated with reduced CT variability, which predicted higher child psychopathology and social withdrawal. Whereas all children exhibited similar initial levels of CT, children of controls reduced CT levels over time while children of depressed mothers maintained high, non-flexible levels. Mother negativity was related to lower initial CT levels, which predicted decreased empathy. Findings suggest that chronic maternal depression may compromise children's social-emotional adjustment by diminishing HPA-system flexibility as well as limiting the mother's capacity to provide attuned and predictable caregiving.

1. Introduction

Maternal depression across the child's first years of life has been repeatedly shown to exert significant negative effects on development, particularly in the domain of social adjustment. Children of depressed mothers tend to be more socially withdrawn (Yan and Dix, 2014), have difficulties acquiring age-appropriate social skills (Carter et al., 2001), and are less competent at forming peer relationships (Maughan et al., 2007). Disruptions have similarly been found in the maturation of physiological systems that support the capacity to manage stress, employ approach orientation, and engage in social relationships, including EEG asymmetry (Peltola et al., 2014), cardiac vagal tone (Gentzler et al., 2012), cortisol response (Dougherty et al., 2013; Waters et al., 2013), and oxytocin production (Apter-Levy et al., 2013). Moreover, offspring of depressed mothers are more susceptible to develop psychopathology in childhood, adolescence, and adult life (Goodman et al., 2011; Gotlib et al., 2014). Yet, the mechanisms by which vulnerability is transmitted to offspring are not fully clear. In the current study, we utilized a birth cohort assessed repeatedly across the first six years to examine pathways by which chronic maternal depression may predict child psychosocial maladjustment as related to hypothalamic-pituitary-adrenal (HPA)-axis functioning and the mother's negative parenting. Three social outcomes were tested at six years; child psychopathology, social withdrawal, and empathy.

One pathway by which maternal depression, affecting approximately 15% of parturient women (Serretti et al., 2006), may impact child vulnerability to stress and psychopathology is via HPA axis functioning (Cicchetti, 2010; Selye et al., 1936). Models on "allostatic load" (McEwen, 1998) have shown that prolonged exposure to early life stress, including exposure to maternal depression (Badanes et al., 2011; Evans et al., 2007; Feldman et al., 2013b), may lead to insufficient glucocorticoid signaling, resulting in

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dysfunctional cortisol (CT) response to daily stressors (Raison and Miller, 2003). Early life stress may lead to hyper- or hypo- CT reactivity combined with reduced variability and flexibility of the system, as expressed in diminished diurnal CT decline and limited decrease in CT levels during a home visit or stressful paradigms (Badanes et al., 2011; Feldman et al., 2013b; Miller et al., 2007), a pattern characteristic of individuals with major depression disorder (Heim et al., 2008). Indeed, alterations in CT patterns have been found in infants exposed to maternal depression during prenatal or early postnatal life (Dougherty et al., 2013; Feldman et al., 2009; Halligan et al., 2004; Hammen et al., 2003; Mackrell et al., 2014; O'Donnell et al., 2013). Infants of postnatally-depressed mothers showed elevated baseline CT levels (Brennan et al., 2008), altered CT response, and inability to reduce CT levels during a home visit (Feldman et al., 2009; Fernandes et al., 2014; Waters et al., 2013). However, as not all studies found links between maternal depressive symptoms and child CT (Essex et al., 2002; Feldman et al., 2014; Pendry and Adam, 2007), it is possible that the effects of depression on the child's HPA-axis functioning is observed only in more severe cases, for instance, when mothers are diagnosed with clinical depression or when depression co-occurs with other risk conditions or negative parenting.

The altered HPA-axis functioning observed in children of depressed mothers may be associated with the compromised psychosocial adjustment observed in these children. Among children of postnatally depressed mothers, higher CT was associated with more social-emotional problems (Palmer et al., 2013), and abnormal CT reactivity and inability to reduce CT levels during a home visit predicted difficulties in social engagement and emotion regulation (Feldman et al., 2009). Mother's prenatal and postnatal depression predicted lower child CT and low CT in turn correlated with externalizing (Laurent et al., 2013a) and internalizing (Laurent et al., 2013b) symptoms. Mackrell et al., (2014) found that among children of depressed mothers, reduced positive emotionality was associated with lower CT reactivity. Importantly, Essex et al. (2002) found that preschoolers exposed to current maternal depression had elevated CT only if they were also exposed to early life stress, highlighting the role of the postpartum period.

Among the most stress-inducing aspects of growing up with a depressed mother is the disruptions to the mother-child relationship in cases of maternal depression (Essex et al., 2002; Feldman et al., 2009; Field, 2008). Depressed mothers often display lower sensitivity (Kim et al., 2011), more negativity and anger (Maughan et al., 2007; Pratt et al., 2015), increased intrusiveness (Murray et al., 2010), difficulties in maintaining physical proximity (Feldman and Eidelman, 2003; Feldman et al., 2004), and inconsistent, unpredictable parenting (Jameson et al., 1997; Leadbeater et al., 1996). These maternal behaviors have been associated with altered child CT patterns (Blair et al., 2008; Feldman et al., 2009; Hastings et al., 2011; Kaplan et al., 2008), suggesting that compromised parenting may be a key factor in the child's psychosocial maladjustment, possibly via its effect on HPA dysregulation. This notion is consistent with research in animal models, which showed that maternal proximity and the species-typical maternal behavior exert a regulatory impact on the pup's stress response by organizing glucocorticoids receptor densities in the hippocampus (Weaver et al., 2004). The mother's inability to provide external regulation to the child's distress is also observed in the high negative emotionality and low emotion regulation found in children of depressed mothers (Blandon et al., 2008; Feng et al., 2008).

As such, the current study examined the associations between persistent maternal depression across the first years of life and the mother's negative parenting with children's psychosocial adjustment at six years as related to the child's CT baseline and variability. We chose to focus on a specific sub-group of depressed mothers not previously studied in depth. Most studies on children of depressed mothers followed clinic samples or mothers with comorbid early life stress, such as poverty, teenage pregnancy, or single motherhood, conditions that carry independent negative effects on development. Our goal was to examine the effects of lasting maternal depression *in and of itself* on the child's physiological and behavioral systems, when all other contextual conditions

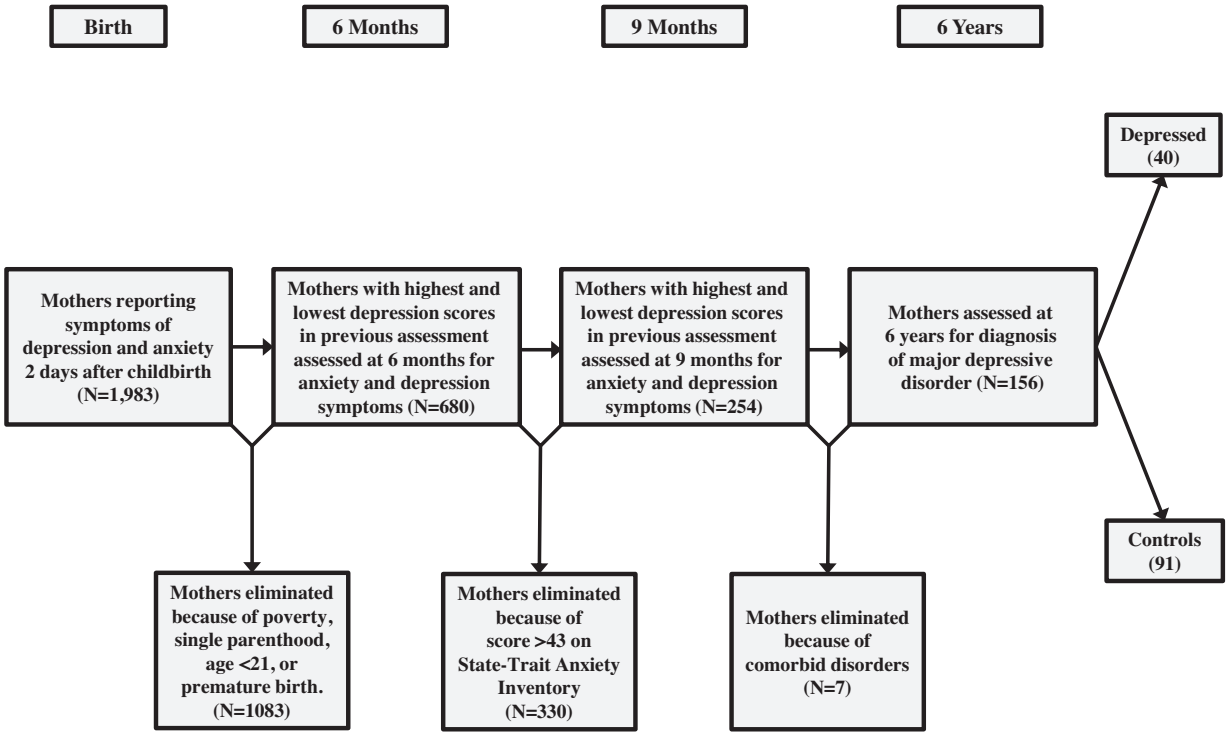


Fig. 1. Recruitment of families from birth to six years.

are low-risk. We recruited a community birth sample of healthy, educated women who were married or cohabitating, above 21 years, and above poverty level who gave birth to a healthy, term, and singleton infant. Maternal depressive symptoms were assessed at birth, six, and nine months and clinical depression was diagnosed at 9 months and at 6 years to form two comparable groups: mothers who reported high depressive symptoms across the first year and were diagnosed with depression at both 9 months and 6 years and controls who reported no elevated symptoms across the same period. Three outcomes were tested at six years: child psychopathology, which has shown to be increased in children of depressed mothers (Goodman et al., 2011); child social withdrawal, described as higher among such children (Dix et al., 2012; Johnson et al., 2013; Stein et al., 1991); and child empathy, found to be lower in children of depressed mothers (Apter-Levy et al., 2013; Zahn-Waxler et al., 1990).

Four hypotheses were proposed; (a) depressed mothers will show more negative parenting, expressed in open negative affect and anger, hostility, depressed mood, and inconsistent parenting. (b) Children of depressed mothers will show more psychosocial maladjustment as indicated by each of the three outcomes. (c) Consistent with research on the effects of early life stress and maternal depression on HPA-axis functioning (Badanes et al., 2011; Feldman et al., 2013b; Gunnar and Donzella, 2002), we expected altered CT patterns in children of depressed mothers. Research has shown that among healthy preschoolers, a decrease in CT levels from baseline measured at the first 10 min of the experiment is observed during a home visit (Davies et al., 2007; de Bruijn et al., 2009; Smeekens et al., 2007). While some of the variability stems from the natural decrease in CT throughout the day (Davies et al., 2007), another portion of the variance has been associated with the mother-child relationship quality, and research has shown that negative mother-child interactions blunt the natural CT decrease (Davies et al., 2007; Smeekens et al., 2007). Since depressed mothers engage in more negative parenting (Maughan et al., 2007; Pratt et al., 2015) and their children show altered diurnal CT patterns (Dougherty et al., 2013), we expected that children of depressed mothers would not display the normative decrease in CT levels during the home visit, leading to what researchers have termed as reduced CT variability (Badanes et al., 2011; Feldman et al., 2013b; Gunnar et al., 2009; Rogosch et al., 2011). Finally (d), applying a latent growth curve model (LGM) using structural equation modeling (SEM), we expected that paths leading from maternal depression and negative parenting to lower child psychosocial adjustment would be related to children's CT baseline and variability, suggesting that one mechanism for the cross-generation transfer of vulnerability may relate to the associations between maternal depression and child HPA-axis functioning.

2. Methods

2.1. Participants

Participants were recruited in five waves of data collection as follows (Fig. 1).

2.1.1. First wave of data collection; Birth

The initial cohort included 1983 women who were consecutive admissions to two university hospitals and were recruited on the second post-birth day. Research assistants visited the maternity wards of two tertiary care hospitals in a large metropolitan area and invited women who were physically healthy by their own account, delivered a healthy term singleton infant (excluding genetic disorders and infants requiring specialized medical care or NICU hospitalization), completed at least 12 years of education, and were cohabitating with the infant's father to participate in a study on maternal postpartum mood. Women completed demographic questionnaires and the Beck Depression Index (BDI; Beck et al., 1961) and State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) questionnaires. Recruitments were conducted twice a week in each ward and 39.8% of the women approached refused participation. Hospital records showed no systematic differences on demographic variables between participating and declining women or between women in the two hospitals. Only mothers who were free of physical illness, completed high-school, were over 21 years, were married or cohabitating, and their infants were healthy, term, and singleton were included. In all families the mother was the primary caretaker for the child. Families were above the poverty line as indexed by income above poverty cutoff (6000 NIS per month, approximately $1800).

2.1.2. Second wave of data collection; Six months

Of the 1983 women recruited at birth we wished to create two comparable cohorts; mothers reporting elevated depressive symptoms across the infant's first year, and mothers who reported low symptoms during the same period. We thus selected women in the high (BDI scores >11) and low (BDI <9) ends of the depressive symptoms continuum at birth to complete measures of anxiety and depression at six months ($N = 900$ approached, $N = 680$ responded-75.5%). No differences related to demographic, medical, or mood factors at birth were found between responding or non-responding mothers.

2.1.3. Third wave of data collection; Nine months questionnaires

From the 680 women who responded at 6 months we again sent questionnaires to those at the high and low ends of the BDI scores at nine months ($N = 350$ approached, $N = 254$ responded-72.5%). Again, no differences related to demographic or medical factors or mothers' mood at six months were found between those who did or did not respond.

2.1.4. Fourth wave of data collection; Nine months home visit

Of the 254 mothers who responded at nine months, we contacted 210 mothers at the high and low ends of the depressive symptomatology who did not report high anxiety symptoms (STAI<43). Of those, 192 agreed to participate in the home visit (91.4%), with no differences in mood variables at 9 months between those who agreed and those who declined. These 192 mothers were assessed by a clinical psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997).

2.1.5. Fifth wave of data collection; Six years home visit

Of the 192 families seen at 9 months, we contacted all families we were able to locate at six years. One-hundred and fifty-six families (81.2%) including mothers, fathers, and children (child age 6.33 ± 1.25, mothers' age 38.66 ± 4.4, fathers' age 41.04 ± 4.74 years) were found and were willing to participate. Those families were visited and attrition was mainly related to inability to locate families. There were no significant demographic or psychopathologic differences between those who dropped out and those who continued. At six years, mothers were again diagnosed by a clinical psychologist using the SCID-I (First et al., 1997) and children were diagnosed using the Development and Well-Being Assessment (DAWBA; Goodman et al., 2000). Seven mothers with comorbid disorders such as anxiety and eating disorders or subclinical depression were excluded from the sample. This led to two final cohorts—46 mothers who reported high depressive symptoms at birth, six, and nine months and were diagnosed with Axis-I depression at both 9 months and six years (depressed group), and 103 mothers reporting no elevated symptoms at any time point and without any psychiatric diagnosis at 9 months and 6 years

Table 1
Demographics information for depressed and non-depressed groups.

	Non-depressed		Depressed	Statistics	
	Mean	SD	Mean	SD	*T* value
Mother education	14.24	2.54	13.97	2.78	0.54, ns
Mother age (years)	37.05	4.12	35.74	4.9	1.76, ns
Father education	13.42	3.24	13.93	2.56	0.88, ns
Father age (years)	39.7	4.56	37.96	5.5	1.51, ns
Child age (months)	76.51	14.69	71.33	13.46	1.84, ns
Child gender			$\chi^2(5) = 0.25$, ns		
Male%	52.7%		57.5%		54.2%
Child birth order			$\chi^2(1) = 3.50$, ns		
Firstborn%	36.2%		54.1%		41.1%

(control group). Of these families, cortisol data was not available for 6 families from the depressed group and 12 families from the control group (e.g., child could not produce enough saliva), leading to a sample of 131 families who provided full data (depressed, $N = 40$, control, $N = 91$). The five waves of data collection leading to the current sample are presented in Fig. 1. No differences in demographic factors were found between the depressed and non-depressed groups (Table 1) or between families with CT data and others in their respective groups. At six years, 80% of the parents had college degree, 91.4% were married, and 89% of the mothers were employed. Among children, 51% were males and 35.5% first born. Two depressed mothers (4%) were treated by medication and four depressed mothers (8.6%) and 10 controls (9.7%) received psychotherapy, with no differences in any study outcome. The study was approved by the Institutional Review Board and all participants signed an informed consent.

2.2. Procedure and measures

Families were visited at home in the afternoon (after 1500 h) hours to control for diurnal variability in CT (Engert et al., 2011) and visits were conducted by two clinical psychologists. After ten minutes of acquaintance, the first salivary sample was collected from the child for baseline (CT t_1). Following, mother and child were separated into two rooms, mothers were administered the DAWBA and then the SCID while the child was administered a neuropsychological test, IQ test, and two empathy paradigms by a different clinician. The two empathy paradigms were designed to expose the child to the experimenter's feigned distress and included "hurting foot" and "sighing painfully". The second salivary sample from the child was collected after the testing and before reuniting with the mother (CT t_2; 90 min from baseline). Next, mother and child were videotaped in a ten-minute interaction with age-appropriate preselected toys, followed by a father-child interaction (10 min) and a triadic mother-father-child interaction (10 min), which ended the visit. Ten minutes after the end of the interactions, the third salivary sample for recovery was collected from the child (CT t_3; 40 min from t_2).

2.2.1. Maternal psychiatric diagnosis

Was conducted at both nine months and six years using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997). Forty-six mothers (29.6%) were defined as chronically-depressed. These mothers showed high depressive symptoms (BDI >11) at birth, six, and nine months, received a clinical diagnosis of MDD at both nine months and six years, and reported being depressed throughout most of the child's first six years. The control group included 103 non-symptomatic mothers (66%).

2.2.2. Child psychiatric diagnosis

The Development and Well-Being Assessment (DAWBA) is a structured interview designed to generate DSM-IV psychiatric diagnoses in children aged 4–16 years (Goodman et al., 2000) based on parent report. The DAWBA has been well-validated, including a large sample in Israel (Mansbach-Kleinfeld et al., 2010). Diagnoses were conducted by clinical psychologists supervised by a child psychiatrist who were blind to all other information. The following diagnoses were assessed in the DAWBA interview; Anxiety Disorders, Oppositional-Defiant/Conduct Disorder, Attention Deficit and Hyperactivity Disorders, Developmental Delay, and Depression. Clinicians conducting the SCID and DAWBA were supervised by a child psychiatrist with inter-rater reliability measures, measured on 25 cases, exceeding 85% agreement on both tests (kappa = SCID= .85, DAWBA = .86).

2.2.3. Hormone collection and analysis

Cortisol collection: Assays were collected at baseline, 20 min after the IQ and neurocognitive testing, a total of 90 min from baseline, and 40 min thereafter (10 min after end of interactions). At each time-point children were asked to chew on a roll of cotton (Salivates—Sarstedt, Rommelsdorf, Germany) until saturation. Salivates were frozen at −20 °C until assayed.

Table 2
Group differences in study variables.

	Depressed ($N = 40$)		Non-depressed ($N = 91$)		
	Mean	SD	Mean	SD	*T*-Test
Maternal negative parenting	1.94	1.03	1.51	0.74	−2.7*
Child social withdrawal	1.49	0.69	1.21	0.3	−3.18*
Child Empathy	4.19	0.87	3.97	0.87	−1.16
Child cortisol time 1 (nmol/L)	2.037	0.711	2.143	0.947	0.63
Child cortisol time 2 (nmol/L)	1.888	0.969	1.829	0.694	−0.39
Child cortisol time 3 (nmol/L)	1.961	0.992	1.790	0.706	−1.12
Child psychopathology		$\chi^2(1) = 32.85$**			
With%	15%		61%		38%

* $p < .01$
** $p < .001$

Cortisol Analysis: Salivates were kept cooled until centrifuged at 4 °C at 1000 × g for 15 min. The samples were then stored at −20 °C until assayed. CT levels were assayed using a commercial ELISA kit (Assay Design, MI). CT levels were calculated by using MatLab-7 according to relevant standard curves. The intra-assay and inter-assay coefficients are less than 10.5 and 13.4 percent, respectively.

2.2.4. Mother-Child interaction

Ten minutes of mother-child interactions with a set of pre-selected toys were filmed (Feldman, 2007a). Interactions were coded with the Coding Interactive Behavior (CIB) manual, a well-validated global system of 45 codes which are aggregated into several constructs (for review, Feldman, 2012a). Two coders, trained to 85% reliability on all codes and blind to all other information, coded the interactions. Inter-rater reliability was computed for 20% of the interactions and reliability was greater than 87% on all codes (intraclass $r = .88–.96$). The *Mother Negative Parenting* and *Child Social Withdrawal* constructs, which have been associated with maternal depression (Dollberg et al., 2006; Feldman et al., 2009; Pratt et al., 2015), were used here. Each rating scale included in the constructs is coded on a scale from 1 (minimal expression of the target behavior during the interaction) to 5 (maximal expression of the target behavior during the interaction). Codes are then averaged into constructs and further analyses is conducted on the constructs, consistent with prior studies using the CIB (Feldman, 2012a).

2.2.4.1. Mother negative parenting—included the following codes. Maternal negative mood/anger, maternal depressed mood, maternal anxiety, maternal hostility, and mother's inconsistent style (alpha = .87). The mother's negative mood codes address overt maternal emotions expressed through verbal and non-verbal modalities, such as anger, depression, and overt sign of anxiety. Mother's hostility is expressed through her tone of voice, "put down" statements, facial expressions, or movements (body position, hand motions). The inconsistent style is observed when mothers shift unpredictably from moments of involvement to disengagement, high to low arousal, and sensitive to rough caregiving.

2.2.4.2. Child social withdrawal—included the following codes. Child social withdrawal and child avoidance (alpha = .85). The social withdrawal scale addresses the child's passive withdrawal from mother and play context, for instance, avoiding eye contact, not initiating conversation, no involvement with toys, or no response to maternal bids. The avoidance scale describes a more active form of withdrawal, such as child distancing him/herself from the mother or clearly expressing displeasure, aloofness, or distance.

2.2.5. Child empathy

Child empathy was coded from the two observational paradigms. In the "hurting foot" paradigm, the experimenter feigned pain in her foot, holding the foot as if she has hurt it on the table or chair. In the "sighing painfully" paradigm, the experimenter pretended to talk on her cell phone and then emitted a long sigh, as if she received some bad news. Each procedure was coded on multiple scales from 1 (minimal amounts of the behavior) to 5 (maximal amount of the behavior). Inter-relater reliability on 20% of interactions was above 90% (intra-class $r = .93$). The empathy construct was the average of two scales over the two paradigms: *maintaining involvement*, and showing *empathic concern*. Maintaining involvement considers the degree to which the child remains involved with the experimenter when she seems to experience pain or receives bad news and does not leave or withdraw. Empathic concern describes overt and active empathy, such as asking what happened or offering assistance. This composite, coded from similar paradigms, was found to reflect a more mature type of empathy (Roth-Hanania et al., 2011).

2.3. Statistical analysis

Prior to analysis, missing values were imputed by regression (less than 10 cases in each variable) and extreme values were explored but not found. CT distributions were sufficiently close to normal and values were not log-transformed. We first explored gender differences but none were found. Differences between groups were examined with *t*-tests and correlations among variables with Pearson's correlations. For our final hypothesis, a Latent Growth curve Model (LGM) using Structural Equation Modeling (SEM; McArdle and Epstein, 1987) was implemented. LGM is considered the preferred method for analyzing changes in a variable measured repeatedly over time (Duncan and Duncan, 2004) and conducting it through SEM enabled us not only to evaluate differences in CT baseline and variability but also to integrate these factors in a path analysis (McArdle and Epstein, 1987). The growth-curve method creates a regression-type line for CT levels over time. Two latent factors were estimated, one representing baseline CT (intercept), the other measuring CT change over time (slope) and this variable was used to index CT variability. To represent baseline CT, the intercept was created with a fixed loading of 1.0 to CT t_1, CT t_2, and CT t_3. To represent CT variability, the slope was created with a fixed 0 loading to CT t_1, a fixed 9.0 loading to CT t_2, and a fixed 13.0 loading to CT t_3, representing the number of minutes between the first and last CT measurements. After the initial growth model, we added the other variables and created a path model to predict the three outcomes. Maternal depression and *Mother Negative Parenting* were set as predictors of child CT intercept and slope. Child CT intercept and slope were set as predictors of *Child Psychopathology, Empathy, and Social withdrawal.* The model was tested using AMOS19 (Arbuckle, 2009). Model fit was assessed using the following goodness-of-fit indices (see Hu and Bentler, 1999); Chi-square (Tabachnick and Fidell, 2007), Normed Fit Index (NFI, Bentler and Bonnet, 1980), Comparative Fit Index (CFI; Rigdon, 1996), and Root-Mean-Square Error of Approximation (RMSEA; Browne et al., 1993). A non-significant chi-square, NFI, or CFI equal to or greater than .95, and an RMSEA less than or equal to .07 (Hu and Bentler, 1999; Tabachnick and Fidell, 2007) reflect a good fit for the data.

3. Results

3.1. Group differences in study variables

Means, standard deviations, and *t*-test analysis are presented in Table 2. Consistent with our hypothesis, depressed mothers exhibited more *Negative Parenting* and their children showed higher *Social Withdrawal*. Contrary to our hypothesis, no mean-level differences were found for *Empathy*. Significant differences emerged in child propensity to psychopathology; among children of depressed mothers 60% received an Axis-I-diagnosis compared to only 15% among children of controls.

In terms of child CT, no mean-level differences were found in CT t_1, CT t_2, and CT t_3. To examine group differences in CT change over time, repeated-measure ANOVAs were computed for each group. Among controls, significant change in CT was found over time, $F(2,180) = 11.83$ $p < .001$. Post-hoc Bonferroni tests revealed significant differences between t_1 and the other two time-points (CT t_1-CT $t_2 = .314$, S.E. = .083, $p < .01$; CT t_1-CT $t_3 = .353$, S.E. = .085, $p < .001$). However, no differences between CT assessments emerged for children of depressed mothers; $F(2,78) = .65$, NS. These findings demonstrate limited CT variability and inability to decrease CT in the presence of the mother and the home environment (Fig. 2).

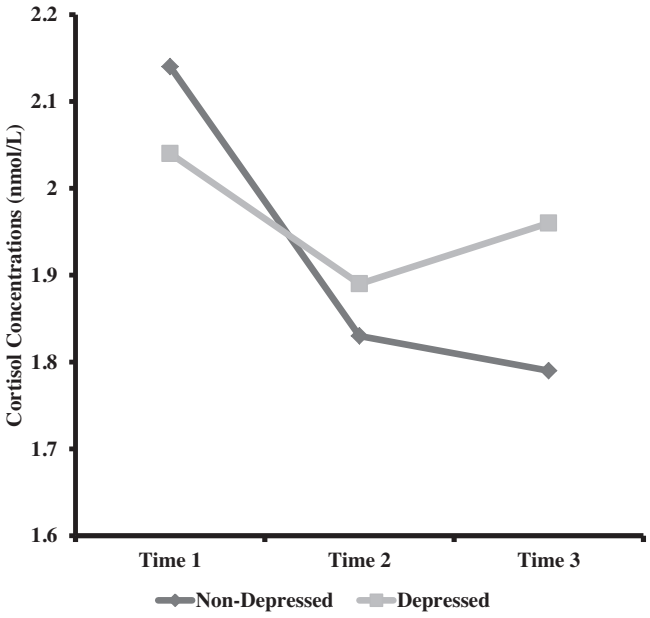


Fig. 2. Child cortisol levels in children of depressed and non-depressed mothers.

3.2. Inter-correlations among study variables

The inter-correlation matrix among study variables is presented in Table 3. As seen, *Child Social Withdrawal* was positively related to *Mother Negative Parenting* and negatively to CT t_1. *Child Empathy* correlated with child CT at all three time-points. *Mother Negative Parenting* was negatively related both to CT t_1 and CT t_2, and *Child Social Withdrawal* was negatively related to CT t_1. The three CT measurements were highly correlated with one another.

3.3. SEM

We first examined the LGM model for the three CT assessments. CT levels significantly dropped in a rate of −.022 nmol/L (SD = .005, $p < .001$) with every 10 min of the experiment. Slope and Intercept were not significantly correlated ($b = -.01$, S.E. = .006, NS), indicating that children with higher levels of baseline CT did not necessarily show greater decline. This model showed a good model fit; $\chi^2(3) = 2.26$, NS; NFI = .98; CFI = 1.0, and RMSEA = .00.

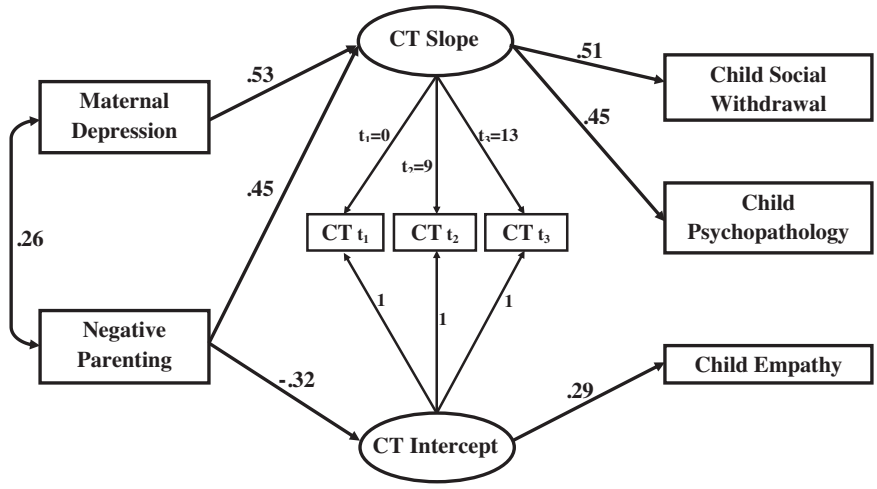
Table 3
Inter-correlations among study variables.

	1	2	3	4	5	6
Maternal negative parenting						
Child social withdrawal	0.38**					
Child empathy	−0.06	−0.04				
Child cortisol time 1 (nmol/L)	−0.19*	−0.18*	0.20*			
Child cortisol time 2 (nmol/L)	−0.23**	−0.07	0.22*	0.56**		
Child cortisol time 3 (nmol/L)	−0.12	−0.13	0.24*	0.53**	0.56**	

* $p < .05$
** $p < .01$

Next, we entered the other variables into the model to examine paths from maternal depression and mother negative parenting to the three outcomes as related to CT baseline and variability. We started by using all possible paths. Following Bentler and Mooijaart, (1989), we arrived at the most parsimonious model by systematically omitting non-significant parameters (Hays et al., 1994). As seen in Fig. 3, maternal depression was negatively related to child CT variability, indicating that children of depressed mothers were less able to reduce CT levels during the home visit as compared to controls. *Mother Negative Parenting* was negatively linked to child baseline CT and positively to CT variability, indicating that the higher the mother's negativity, the smaller the decline in CT levels across the home visit. CT variability predicted *Social Withdrawal* and psychopathology; lower CT variability was associated with greater propensity for psychopathology and higher *Social Withdrawal*. Finally, baseline CT was related to *Empathy;* children who had greater initial CT levels were more empathic to the distress of another person. Overall, the model had a good fit to the data: $\chi^2(21) = 19.42$, NS; NFI = .90; CFI = 1.0, and RMSEA = .00.

To examine whether the model would differ by the nature of the child's psychopathology, we ran the model once using internalizing (anxiety, depression) and once using externalizing (conduct/ODD,



$\chi^2(21)=19.43$, NS; NFI=.90; CFI=1.0; RMSEA=.00.

Fig. 3. Results of a latent growth curve model embedded within a structural equation model.
Model tests the effects of maternal depression and negative parenting on children's social adjustment as related to child baseline CT (Intercept) and CT variability (Slope). All coefficients shown are significant ($p < .05$). Index: CT t_1 = child cortisol at first assessment (10 min after home arrival in nmol/L), CT t_2 = child cortisol at second measurement (90 min after CT t_1 in nmol/L) CT t_3 = child cortisol at third assessment (40 min after CT t_2 in nmol/L).

ADHD) disorders. The two models were similar and no marked differences in beta weights were found for any path.

4. Discussion

Although much research attested to the negative effects of maternal depression on children's mental health, longitudinal studies integrating repeated diagnosis, direct observations, and neuroendocrine markers are less common. For a more comprehensive perspective, the next step in understanding the impact of maternal depression on the developing child requires further specificity; what are the parenting components impaired by depression, how are they linked with altered functioning of physiological support systems, and are these disruptions associated with the child's adaptation to the social world. Such models may construct a more nuanced perspective, help describe why some children of depressed mothers fare better than others, and highlight factors that should become the target of intervention. Prior to discussing our findings it is important to note that the terms "predict" or "leads to" describe statistically significant paths, not causal effects, particularly as mother-child interaction and the social outcomes were both measured at six years.

Our sample addresses a specific group of mothers with chronic depressive symptoms but with otherwise low-risk contextual conditions. While the exclusion of mothers with comorbid anxiety is certainly a study limitation for the generalizability of the findings, our sample may provide a first step in understanding the relations between chronic maternal depression without comorbid risk and the child's HPA-axis functioning and social outcomes. Our findings show that while no mean-level differences emerged between groups for any CT assessment, maternal depression was associated with reduced child CT variability, as indexed by no significant decrease in CT levels across the home visit as compared to the significant decrease found for controls, suggesting disruptions to HPA-system flexibility. Research has shown that among healthy preschoolers, a decrease in CT levels from baseline is observed during a home visit as quickly as 20 min from the initiation of the visit (Davies et al., 2007; de Bruijn et al., 2009; Smeekens et al., 2007). In contrast, our children of depressed mothers did not show a significant decrease in CT levels during the 2.5-hour visit. Prior research has shown that such decrease is related to both natural diurnal variations in CT (Davies et al., 2007) and the degree of negativity during mother-child interactions (Davies et al., 2007; Smeekens et al., 2007). Thus, the blunted CT decline found here may index failure of the maternal presence to buffer the child's HPA response. Interestingly, Gunnar et al. (2009), reviewing the effects of various paradigms on changes in CT, suggest that in young children, particularly during the preschool years, the most potent factor for predicting CT variability is the child's ability to rely on the caregiver's support. Limited CT flexibility, when the system is set at a certain point and does not respond to momentary stressors or their removal, is observed in various conditions involving early life stress (Badanes et al., 2011; Feldman et al., 2013b; Gunnar et al., 2009; Rogosch et al., 2011). Our findings are unique by pinpointing maternal depression *in and of itself* as associated with the same HPA-axis profile as that observed in early life stress, even when contextual risk is minimal and mothers do not suffer comorbid anxiety. The inconsistency between our findings and those showing additional alterations in the child's baseline CT may relate to the multi-risk nature of most samples as compared to the low contextual risk of our children where chronic maternal depression was the only stressor.

Maternal depression was related to children's HPA functioning not only directly but also through its effects on negative parenting. Depressed mothers displayed more negative affect, open anger, hostility, anxiety, and depressed mood during interactions with their children, often shifting unpredictably between moments of negative mood/anger and moments of withdrawal. Such maternal style, typical of depressed mothers (Dix et al., 2012; Stein et al., 1991), may be especially harmful for the consolidation of HPA-system functioning. In such cases, children are not only deprived of the mother's positive external-regulatory components - the sensitive parenting that promotes security and supports maturation of the social brain (Carter, 2014; Feldman, 2012b) – but must maintain constant vigilance and adapt to erratic changes in the mother's mood and behavior. As seen, the mother's negative parenting predicted both CT baseline and variability, charting a profile of *low* baseline CT combined with minimal variability over time and social tasks. The most common explanation for such low baseline and flattened curve is the "allostatic overload" model, which theorizes that prolonged stress leads to system exhaustion, inflexible hormonal production, and glucocorticoids insufficiency resulting in decreased CT bioavailability and, in extreme cases, hypocortisolism (McEwen, 1998; Raison and Miller, 2003). Consistently, studies have found that school-aged children exposed to maternal depression combined with extreme early adversity showed hypocorticolism during a home-visit (Badanes et al., 2011), and toddlers of prenatally-depressed mothers showed decreased CT reactivity when also carrying the risk allele on the glucocorticoid receptor gene (Velders et al., 2012). Thus, hypocortisolism, reflecting a more pronounced disruption to HPA functioning, seems to occur only when several risk conditions coalesce. Our findings similarly show that when maternal depression is combined with overt negative parenting, risk to HPA-axis functioning may increase. Since early affiliative bonds in mammals shape the maturation of the HPA system (Loman and Gunnar, 2010; MacLean et al., 2014; Meaney and Szyf, 2005) and higher CT reactivity and recovery in toddlers were found to predict better attention and mental health at school age (Blair et al., 2008), these findings should raise concern. Moreover, because the mother's parenting style has shown to be individually stable from infancy to adolescence, including stability of the intrusive/negative style (Feldman, 2010; Feldman et al., 2013a), the mother's expressed negative affect and inconsistent behavior should become the focus of parenting interventions already in the first months of life.

Maternal depression was associated with reduced child CT variability and the reduced variability, in turn, predicted child social withdrawal and psychopathology; the lower the variability, the greater propensity for child Axis-I disorder and social withdrawal upon school entry. This is consistent with models suggesting that a central mechanism by which early stress shapes long-term outcomes, including health, well-being, and social functioning, is by re-organizing the brain's glucocorticoid system and HPA-axis functioning (Cicchetti, 2013; Gunnar and Donzella, 2002; Heim and Binder, 2012). Social withdrawal in infants and preschool-aged children has been found to predict more social-emotional problems and psychopathology (Guedeney et al., 2014; Yan and Dix, 2014). We found that social withdrawal was higher in children of depressed mothers and correlated with the mother's negative style, consistent with previous research (Dix et al., 2012; Stein et al., 1991). It is thus possible that children with a biological propensity for social withdrawal and behavior inhibition who are reared by more negative mothers are less able to develop flexible HPA-system functioning which may lead to a socially-withdrawn style that places these children at a greater risk for later psychopathology (Fox and Pine, 2012). This hypothesis, however, should be tested in longitudinal research.

Child empathy was related to maternal depression and HPA functioning in yet another way. While no mean-level differences in empathy were found between children of depressed and non-depressed mothers, maternal depression was related to negative

parenting, which predicted lower child baseline CT and these low levels, in turn, predicted decreased empathy. Children who had higher baseline CT showed more empathic concern and maintained engagement when the stranger was in distress. This type of empathy, measured with similar behavioral paradigms, was found to be stable from infancy to toddlerhood and to predict prosocial behaviors (Roth-Hanania et al., 2011). Higher CT has been associated with more child-initiated social interactions, social competence, and popularity in school-aged children (Tennes et al., 1986), and children and adolescents with low basal CT were found to display more callous- antisocial behavior (Shirtcliff et al., 2009). Lower basal CT has also been associated with diminished activations of the anterior cingulate cortex (Liberzon et al., 2007), a key node of the brain's empathy matrix (Decety, 2014). Intranasal CT administration enhanced activity in the empathy matrix in response to viewing others' pain (Stark et al., 2006), suggesting that sufficient CT reserve may be required to activate the brain's empathic response to the distress of others. Child empathy develops on the basis of attuned parenting; maternal and paternal response to preschoolers' distress was found to predict greater empathy to others' distress (Davidov and Grusec, 2006), and higher mother-infant synchrony across the first year predicted child empathy at 6 and 13 years (Feldman, 2007b). As children's emotion regulation abilities have consistently been shown to predict empathy (Eisenberg et al., 2011), it is possible that the depressed mother's inability to provide attuned parenting disrupts the development of empathy in the child but this hypothesis requires much further research.

With regards to the increased risk for Axis-I psychopathology among children of chronically-depressed mothers upon school entry, our findings are consistent with much prior research demonstrating increased psychopathology in children, adolescents, and adults exposed to early maternal depression (Goodman et al., 2011). Our findings contribute to this literature by showing that chronic maternal depression across the child's first years is associated with reduced HPA-system flexibility, and that such flattening of the system's variability is related to the emergence of psychopathology in the child (Heim et al., 2008). Interestingly, the paths leading from maternal depression via compromised CT variability to psychopathology were similar for children with externalizing and internalizing disorders, suggesting that these paths render children more vulnerable to psychopathology in general, and other factors, such as genetic makeup, parental behavior, or social and cultural factors may play a role in determining the nature of the disorder.

Limitations of the study are numerous and should be considered in the interpretation of the findings. First, although co-morbidity between depression and anxiety is high, we chose to eliminate mothers with comorbid anxiety disorders as a first step, in order to test the effects of depression on the child independent of comorbidity. Depression and anxiety often have opposite effects on maternal behavior and physiological systems (e.g., oxytocin) and we thus chose to eliminate anxiety as a first step. Our findings therefore pertain to a sub-group of depressed mothers and future research is required to examine the generalizability to mothers with comorbid anxiety. Furthermore since we aimed to study the long term effects of chronic maternal depression, we were forced to eliminate many of the women in the sample and were left with a relatively small sample of depressed mothers. Our findings should therefore be replicated in women with remitted depression. Another limitation is that at birth and six months, we measured mother-reported depressive symptoms, not clinical diagnoses. Additionally, we did not test for early life stressors other than social-economical-status and major health issues. Similarly, we only checked for major sources of stress between 1 and 6 years, including divorce, death, or major illness in the family, and other forms of stress across this period could have affected the findings. Another limitation is that we did not collect systematic data during the prenatal period and prenatal depression may have played an important role in the consolidation of the child's HPA functioning. Mother-child interactions were sampled at the same time of CT assessment, limiting our ability to discuss longitudinal associations. Furthermore, child psychopathology was measured by maternal interview and since major depression is associated with more negative perceptions this could have increased the prevalence of psychopathology. Although this is unavoidable, as clinical diagnosis of young children always involves interview of the primary caregiver, it should be taken into consideration. In addition, although salivary cortisol is a well accredited methodology this is a peripheral measure and may not reflect actual central nervous system activity. Finally our findings remain to be integrated with the vast network of variables that act within the central nervous system and thus our knowledge and ability to understand and work with the multiple arrays of factors involved is necessarily limited. Much further research is needed to fully understand how maternal depression shapes children's stress physiology and compromises social adjustment. Such understanding can advance our efforts to construct specifically-targeted early interventions to help mothers adapt a more sensitive parental style that can provide a well-suited framework for their children's growth and development.

5. Contributor

Drs. Apter-Levi, Vakart, and Feldman Michal collected data and conducted psychiatric diagnosis to mother and child.

Dr. Zagoory-Sharon supervised hormonal analysis.

Dr. Pratt analyzed data and co-wrote the paper.

Dr. Feldman Ruth designed study, supervised data collection and analysis, and co-wrote the paper.

6. Financial disclosure

Drs. Apter-Levi, Vakart, Feldman, Zagoory-Sharon, and Feldman have no conflict of interest to disclose.

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