IDENTIFYING THE PATHOPHYSIOLOGY OF DEPRESSION AND ITS PERMEABILITY ACROSS THE LIFESPAN

by

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To my advisor, whose diplomacy, influence, and scientific brilliance I hope to emulate,
To my friends, whose unwavering support deserves much more than words can capture,
To my family, who instilled in me the importance of diligently pursuing dreams and service,
To my spouse, who never lets me take myself too seriously,
And to my sons, who this is all for,
I dedicate the culmination of my work to date.

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ABSTRACT

Major depressive disorder (MDD) and risk for its development are characterized by reduced reactivity and flexibility to environmental demands. Frontal alpha asymmetry (FAA), heart rate variability (HRV), and salivary cortisol reactivity are each well-established indicators of regulation across neural, autonomic, and hypothalamic-pituitary-adrenal (HPA) physiological systems, respectively. Growing literature suggests that each of these processes is dysregulated in individuals with a history of MDD. However, patterns of dysregulation across these physiological systems and relative MDD risk are unknown. Moreover, these physiological regulatory patterns may extent beyond markers of MDD risk in adulthood to also capture the transmission of risk for MDD from parent to offspring. The following series of five studies investigated the pathophysiology of MDD and the permeability of risk across the lifespan. First, the pattern of dysregulation across physiological indices—representing neural, autonomic, and HPA functioning—in adults was examined with regard to depressive symptoms. Second, the associations amongst infant FAA, HRV, and cortisol reactivity and maternal depressive symptoms were assessed as potential early markers of depression risk. Third, mother-infant associations across physiological indices were investigated to assess direct intergenerational transmission of depression risk. Studies 4 and 5 further investigated pathophysiological functioning in mothers and infants within the context of comorbid anxiety and current depressive symptomatology versus lifetime MDD illness. Mothers and their 12-month-old infants (n = 35 dyads) completed resting-state and stressor tasks to assess regulatory patterns across neural, autonomic, and HPA systems, associations with MDD, and intergenerational transmission. In adults, results suggest that lifetime history of MDD is significantly associated with blunted cortisol reactivity; FAA and high-frequency HRV also demonstrated the same direction of associations. In infants, results demonstrated that maternal depressive symptoms, particularly current symptoms, relate to blunted physiological regulation in infants specifically for FAA and HRV indices. For mothers and infants, there was support for the direct intergenerational transmission of FAA and HRV indices. These intergenerational associations did not fully account for intergenerational risk of depression, as maternal physiological regulation and maternal depression were found to each significantly predict infant regulation as simultaneous predictors. Accounting for comorbid anxiety and examining current symptoms versus lifetime illness were essential to investigating associations amongst

physiological functioning and depression. These patterns in conjunction with the literature suggest a developmental model to MDD pathophysiology that encompasses multiple theoretical frameworks. Future research is necessary to clarify regulatory patterns across physiological systems within individuals and across time with regard to MDD risk, onset, and course.

INTRODUCTION

Depression is one of the leading causes of non-fatal disease burden worldwide (Ferrari et al., 2013; Ustün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004) and even mild depressive symptoms are estimated to result in an economic burden of billions of dollars annually (McTernan, Dollard, & LaMontagne, 2013). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), cardinal symptoms of depression are persistently low mood and anhedonia (American Psychiatric Association, 2013); however, growing research suggests depression is characterized by a broad experiential deficit, wherein momentary emotional reactivity breaks down, such that individuals with depression report reduced reactivity to external environmental stimuli across self-report, behavioral, and physiological domains (Bylsma, Morris, & Rottenberg, 2008; Gross, 1998).

Meta-analytic work on emotional reactivity in depression supports the emotion context insensitivity (ECI) model (Bylsma, Morris, & Rottenberg, 2008), a conceptual framework wherein individuals with depression exhibit less reactivity to emotional stimuli in the external environment. Dampened reactivity across valence contexts (i.e., both pleasant and unpleasant stimuli) is theoretically an evolutionarily adaptive response to environments where continued effort may be ineffective (e.g., wherein reactivity would lead to wasted energy) or harmful (Nesse, 2000; Proudfit, Bress, Foti, Kujawa, & Klein, 2015; Rottenberg, 2005; Rottenberg & Hindash, 2015). This conceptual framework is a stark contrast to more classic theories related to emotions in depression, namely the negative mood-potentiation hypothesis, which theorizes preferential processing of negative stimuli during periods of low mood (Beck, 1967). Support of ECI over this classical theory first began with self-report (e.g., less reported sadness) and behavioral observations (e.g., less crying) after experimental mood inductions, with the observation that blunted emotional reactivity was best demonstrated when baseline (i.e., reactivity to neutral stimuli) was also taken into account. In other words, differences in emotional reactivity between individuals with depression and controls have most widely been demonstrated as decreased differences between reactivity to emotional and neutral stimuli for the depressed individuals. These important observations led ECI theorists to postulate that perhaps it isn't only blunted reactivity per se that characterizes depression, but rather a decreased flexibility to changes in the ongoing emotional context of the environment (Rottenberg & Hindash, 2015).

A related theory from the evolutionary-developmental literature also posits that lack of flexibility to environmental demands is the underlying factor for a range of disorders. Specifically, the adaptive calibration model (ACM) states that coordinated defensive activation across systems is necessary to prosper across different life challenges, and that individuals develop dispositional physiological responses to best fit the challenges of their environments (Del Giudice, Ellis, & Shirtcliff, 2011). Extending this framework to depression, the ACM posits that internalizing psychopathology is characterized by lack of coordination across systems rather than overall blunted responsiveness, as suggested by ECI. Substantial research in healthy organisms has demonstrated that neural, autonomic, and hypothalamic-pituitary-adrenal (HPA) systems work in synchrony to coordinate adaptive coping to the environment (Cerqueira, Almeida, & Sousa, 2008; Davidson et al., 2002). In depression, regulation in each of these systems seems to break down (Davidson et al., 2002), though whether this is the result of broad dysregulation across systems within participants or specific dysregulation in different, individual systems across participants is unknown. To date, work assessing coordination of the autonomic system and HPA axis within an adolescent sample supports the ACM in the development of internalizing and externalizing psychopathology broadly (Nederhof, Marceau, Shirtcliff, Hastings, & Oldehinkel, 2015). Specifically, the researchers found that high HPA reactivity (as measured by salivary cortisol) *and* low parasympathetic nervous system reactivity (as measured by respiratory sinus arrhythmia) were predictive of depression onset in adolescent boys (Nederhof et al., 2015). The coordinated nature of dysregulation across autonomic, HPA, and neural systems in adults remains untested.

Delving into the literature concerning physiological indicators of emotional reactivity in depression, support for either of the two proposed theories, ECI and ACM, is difficult to separate. In accordance with the ECI hypothesis, research has demonstrated that physiological reactivity across multiple systems is blunted in depression. However, these studies seldom analyze multiple systems within the same sample, and thus it is possible the demonstrably blunted reactivity in one system (e.g., neural activity) may also relate to a lack of coordination across responses (e.g., HPA axis or autonomic) as posited by the ACM. For instance, emerging evidence links depression to abnormal environmental responsiveness across multiple physiological systems including: low heart rate variability (HRV; Kemp et al., 2010), decreased cortisol reactivity (Burke, Davis, Otte, & Mohr, 2005), and blunted emotion-related neural reactivity [electroencephalogram (EEG)/event-related potential (ERP) (Foti, Olvet, Klein, & Hajcak, 2010; Hill, South, Egan, &

Foti, 2019; Proudfit et al., 2015)]. These processes collectively reflect regulation of responses to environmental stimuli and dysregulation of these processes may increase risk for depression (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Izard, 2010). Utilizing multiple physiological indicators within one sample is the only way to test the assumptions of both the ECI and ACM theories. Moreover, previous research in healthy organisms suggests that neural, autonomic, and HPA processes have bidirectional relationships (Cerqueira et al., 2008; Davidson et al., 2002; Del Giudice et al., 2011). Thus, assessing one regulatory system in isolation may lead to incomplete and possibly inaccurate interpretations of the physiological dysregulation underlying depression. For example, although individuals with depression may differ based on dysregulation across physiological systems or deficits within a number of single systems, previous studies assessing only one physiological indicator would miss these differences—ultimately leading to incorrect conclusions.

The current collection of studies utilizes three physiological indicators within the same sample in order to assess the coordination, or lack thereof, of regulation across systems in depression. Indicators selected for the current studies were based on substantial support of relationships with depression in the literature, feasibility, and participant comfort (e.g., each of these measures are more affordable than functional magnetic resonance imaging, for example, and amenable for developmentally appropriate modifications for both adult and infant assessments, relevant to Studies 2 and 3). For these reasons, the literature relevant to EEG, a direct measure of brain activity used to assess neural responses; electrocardiogram (ECG), a measure of heart activity used to assess coordinated autonomic nervous system function; and salivary cortisol, a measure of HPA axis activity, and each of their relationships with depression is described below.

EEG data can be used to capture frontal alpha asymmetry (FAA), which is brain activity in the alpha band (8-13 Hz in adults) across frontal electrode sites, to assess relatively stable individual differences in emotional responsiveness (Gotlib, Ranganath, & Rosenfeld, 1998; Tomarken, Davidson, Wheeler, & Doss, 1992). Left-sided brain activation indicates present state positive affect, higher levels of trait positive affect, and approach motivation; right-sided brain activation is indicative of state negative affect and withdrawal from the surrounding environment (Davidson, Saron, Senulis, Ekman, & Friesen, 1990; Davidson, 1992; Harmon-Jones & Gable, 2017; Reznik & Allen, 2018). Recent work has demonstrated that increases in left-sided activation correspond with reductions in negative affect and increase in immune function (Davidson et al.,

2003). Meta-analytic work supports that reduced FAA, reflective of reduced left-sided brain activation, is a well-established marker of depression in adults (Thibodeau, Jorgensen, & Kim, 2006). Moreover, reduced FAA seems to be a trait marker of depression vulnerability, rather than solely a marker of clinical state, in that FAA is reduced among individuals with a lifetime history of depression, prospectively predicts depression onset, and is reduced in offspring of mothers with depression (Allen & Reznik, 2015; Allen & Cohen, 2011; Allen, Urry, Hitt, & Coan, 2004; Gotlib et al., 1998; Nusslock et al., 2011; Peltola et al., 2014; Thibodeau et al., 2006; Urry, Hitt, & Allen, 1999).

In addition to neurophysiological data, HRV provides a measure of beat-to-beat changes in heart rate measured by ECG. HRV is a marker of adaptation to continuously changing environmental demands; thus, low beat-to-beat variability is indicative of difficulty responding to and engaging with the surrounding environment (Bigger et al., 1988) and high HRV facilitates calm states and social interaction (Porges, 2009). Variability in heart rate is influenced by both the parasympathetic and sympathetic nervous systems—with high frequency HRV (HF-HRV; also referred to as respiratory sinus arrhythmia; RSA) representing parasympathetic activity at respiratory frequencies, low frequency HRV (LF-HRV) primarily reflecting sympathetic activity, and the low frequency over high frequency ratio (LF/HF HRV ratio) arguably estimating the interplay of the sympathetic and parasympathetic systems (Shaffer & Ginsberg, 2017). HRV is low in depression—indicating difficulty engaging with external demands—to such a degree that HRV in patients with depression more closely resembles recent heart transplant recipients than healthy controls (Nahshoni et al., 2004). This mechanism has been suggested as the causal link between depression and increased autonomic mortality (Carney et al., 2001), and seems to be primarily driven by decreases in parasympathetic activity as indicated by reduced RSA and increased LF/HF HRV ratio (Kemp et al., 2010). Similar to FAA, HRV patterns in offspring of mothers with depression show concordant patterns across rest and reactivity recordings as the mothers, suggesting possible intergenerational transmission of autonomic regulatory patterns that increase risk for depression (Yaroslavsky, Rottenberg, & Kovacs, 2014).

Lastly, salivary cortisol reactivity provides a moment-to-moment assessment of HPA output thought to reflect the adaptive flexibility of the stress response system (Adam, 2012). The temporal dynamics of salivary cortisol stress responses generally maintain three levels: basal (pre-stressor), stress reactivity (wherein cortisol increases in response to a stressor, generally occurring

between 10 and 30 minutes post-stressor), and recovery (lasting from the peak response through return to baseline, between 10 and 30 minutes subsequent to reactivity; Kirschbaum & Hellhammer, 1994). It has been suggested that cortisol is the operating link between chronic stress and disease onset for a multitude of ills, including depression (Bjorntorp & Rosmond, 1999; Epel et al., 2000; McEwen, 2000; Sephton & Spiegel, 2003). Indeed, young children of mothers with severe depression have demonstrably blunted cortisol across basal and reactivity periods (Fernald, Burke, & Gunnar, 2008) and meta-analytic results in adults demonstrate that severe depression is characterized by less fluctuation in cortisol across the three collections, indicating decreased flexibility and adaptation to surrounding environments (Burke et al., 2005). This general pattern of decreased flexibility in cortisol reactivity is consistent with the flattened diurnal cortisol patterns, a separate indicator of HPA functioning, found in depression, though the literature regarding diurnal patterns is mixed (Doane et al., 2013; Heaney, Phillips, & Carroll, 2010; Shirtcliff & Essex, 2009).

The broadly attenuated flexibility described throughout these literatures is consistent with the ECI model (Bylsma et al., 2008); however, not all physiological indices seem to be blunted in depression. For example, mild depression in adults is characterized by high levels of cortisol in the recovery phase, perhaps indicating poor emotion regulation (i.e., failure to return to baseline) rather than overall withdrawal (Burke et al., 2005). It is therefore unclear if depression is characterized by (1) diminished responsiveness to environmental changes consistently across systems (supporting ECI) or (2) diminished responsiveness as measured by one indicator due to inconsistency across systems (supporting ACM).

The following series of studies investigated the pathophysiology of depression and its permeability across the lifespan via three proposed studies. First, I investigated the patterns of regulation across physiological systems in relation to depressive symptoms in adults. Specifically, Study 1 examined patterns across neural, autonomic, and HPA systems with respect to ECI and ACM frameworks. Next, I investigated regulatory patterns across physiological systems in infants to investigate if these indices may serve as early markers of depression risk. Specifically, Study 2 examined patterns across neural, autonomic, and HPA systems in infants with respect to maternal depressive symptoms. Thirdly, I investigated the associations between physiological regulatory patterns in mothers and infants, as dyadic associations of these regulatory patterns may indicate direct intergenerational transmission of depression risk. Specifically, Study 3 examined dyadic

patterns across each physiological system and the possible moderating role of depression. Finally, the current series of studies were supplemented with exploratory analyses (i.e., Studies 4 and 5) to further investigate pathophysiological functioning in depression within the context of comorbid anxiety and current symptomatology versus lifetime illness, respectively.

STUDY 1

The central tenet of the current study is that each of these physiological indicators (FAA, HRV, cortisol reactivity) contributes significant, though incomplete, information regarding depression symptomatology. Quantifying a profile of physiological functioning across systems may better capture environmental responsiveness patterns in depression than focusing on any one system in isolation. Study 1 sought to assess how the coordination, or lack thereof, of regulation across physiological systems relates to depression in adults. First, bivariate correlations assessed relations amongst all physiological measures and current maternal depression. Based on the literatures for each physiological indicator and the overarching ECI framework, I hypothesized that current depressive symptoms would be associated with blunted engagement across physiological measures (FAA, HRV, and cortisol reactivity). For HRV, I predicted negative associations with depression would be strongest for RSA. Next, follow-up analyses regressed current maternal depression scores onto physiological indicators as simultaneous predictors to assess the overall variance jointly accounted for by the indicators as well as the unique effects of each physiological indicator. In the regression analyses, HRV was operationalized specifically as RSA, as RSA and depression history have the largest effect in the literature (Kemp et al., 2010). I hypothesized that each physiological indicator would offer unique information in predicting depression.

Method

Participants

Mothers from a total of 37 mother-infant dyads participated in the current study as part of Dr. Kelleher's ongoing Infant Development Study, which examines how children develop from infancy to preschool. An additional 26 families agreed to participate in the study; however, 17 met exclusion criteria and 9 were unable to complete the study due to availability restrictions. Mother-infant dyads were recruited from areas surrounding Purdue University via fliers, community outreach, and Internet advertisements. Lifetime clinical diagnoses were monitored throughout data collection to ensure that a range of depressive symptomatology was captured such that one third

of the sample consisted of mothers with a lifetime clinical diagnosis of Major Depressive Disorder (MDD) and one third of the sample endorsed no current or historical Major Depressive Episode. The research team was prepared to administer additional screening procedures and targeted recruitment specific to depressive symptomatology if necessary; however, the community sample met proposed thresholds without these procedures. Comorbid disorders were allowed within the subgroup of participants with lifetime history of MDD to increase feasibility of the project and, relevant to Studies 2 and 3, previous research suggests that maternal psychopathology alongside contributing environmental factors may be non-specific in increasing the likelihood of offspring depression (Caspi et al., 2003; Kendler et al., 1995; Mitchell, McCauley, Burke, Calderon, & Schloredt, 1989; Puig-Antich et al., 1989; Sullivan, Neale, Kendler, 2000). Relevant to Studies 2-3, dyads were excluded if the mother was not the biological mother of the infant participant or if English was not the primary language spoken at home.

Of the 37 mothers who participated, two were not able to complete laboratory tasks or clinical assessment due to time constraints, one mother declined participation in EEG recording, four mothers' ECG data was lost due to equipment failure, and seven mothers' cortisol data was lost due to one of several factors (e.g., declined stressor task, mother/baby would not separate, time constraints). Thus, of the 35 mothers who completed laboratory tasks, 97.1% of FAA (n =34), 88.6% of HRV (n = 31), and 80% of cortisol reactivity (n = 28) values were available for analyses; 24 mother participants had complete psychophysiological data. Participation was voluntary, and mothers were compensated for participation. The Purdue University Institutional Review Board formally approved this research.

Procedures

Data collection occurred across two laboratory sessions and an at-home survey. Each laboratory session was 3-4 hours in length and sessions were completed approximately one week apart. Relevant to the current series of studies, the first laboratory session consisted of consent procedures, parent interview regarding infant development, and infant physiological assessments. In the second laboratory session, researchers reviewed consent and conducted maternal clinical and physiological assessments while simultaneously completing infant developmental assessments. The DASS-21 clinical assessment was completed as part of the at-home survey, which was typically completed within one week of the first laboratory session. For clarity, overall procedures

relevant across current Studies 1-3 are illustrated in Figure 1. Details pertinent to each of the current studies are explained in their respective Methods sections.

Clinical Assessment

Structured Clinical Interview for DSM-5 (SCID-5). The SCID-5 (First, Williams, Karg, & Spitzer, 2015) is a clinical interview that assesses for the presence of current and historical psychological disorders. Administration was limited to Modules A-G, which includes mood, substance use, anxiety, obsessive-compulsive concerns, and a screener for symptoms related to psychosis. Feeding and eating, adult attention-deficit/hyperactivity disorder, and trauma- and stressor-related disorders were not included. Additionally, in light of research concerning the importance of prenatal exposure to maternal depressive symptomatology (Marceau et al., 2016), the SCID-5 was supplemented with an expanded Module A: Mood Episodes assessment to evaluate relation of episodes to pregnancy and birth, and Module E: Substance Use assessment to evaluate medication usage during pregnancy (e.g., SSRIs). Clinical psychology graduate students, trained in the administration, scoring, and interpretation of this measure, administered all SCID-5 interviews.

Depression Anxiety Stress Scales (DASS-21). The DASS-21 is a 21-item self-report measure that assesses symptoms of depression, anxiety, and stress over the past week (DASS-21; Lovibond & Lovibond, 1995). The DASS-21 conceptualizes depression as low positive mood, anxiety as physiological arousal, and stress as non-specific negative affect that is common to both depression and anxiety. Mothers completed the DASS-21 at home as part of a larger survey. In the current sample, one participant was removed from analysis as a statistical outlier (i.e., > 3 SD);[1] internal consistency was found to be in the fair to good range (depression: Cronbach's $\alpha = .80$; anxiety: Cronbach's $\alpha = .70$; stress: Cronbach's $\alpha = .83$).

Physiological Assessment: Mother Laboratory Tasks

Mother participants completed a resting-state task during which continuous EEG and ECG were recorded. Participants were seated alone and were not instructed to close their eyes. Mother

[1] Of note, this participant did not meet criteria for lifetime history of any mood or anxiety disorder.

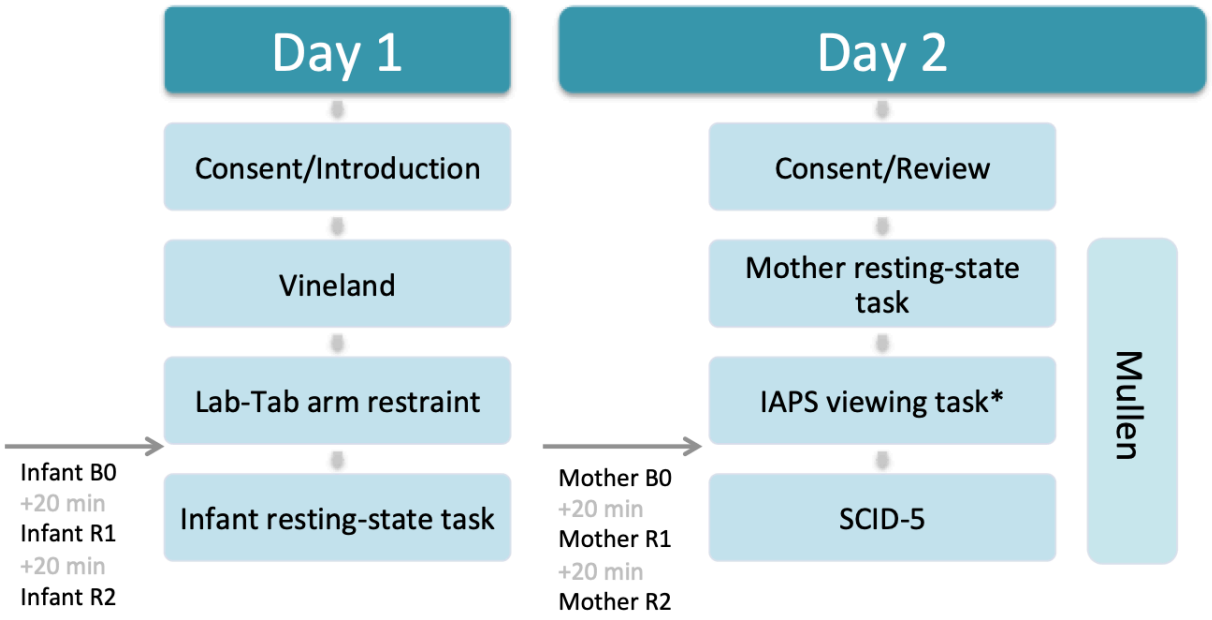

Figure 1. Depiction of all procedures across both assessment days, utilized across Studies 1-3. The DASS-21 clinical assessment was completed by mother participants as part of the at-home survey, which was typically completed within one week of the first laboratory session. *The IAPS viewing task was counterbalanced with a cognitive processing task as part of a separate study.

participants were instructed to passively view a silent video consisting of moving blobs for three minutes with booth lights remaining on.

Mother participants also completed a passive viewing task of neutral and emotionally provocative images selected from the International Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2005). Previous work indicates that the passive viewing of IAPS images elicits cortisol reactivity in adults (i.e., Luo, Xiao, Miao, & Luo, 2012). The present task consisted of 6 blocks of 20 images each that varied on valence and arousal according to ratings provided in the IAPS manual (Lang et al., 2005). Images were selected such that valenced blocks (pleasant and unpleasant) were matched on arousal, and images presented in neutral blocks were significantly less arousing. Blocks were presented in a set order (neutral, pleasant, unpleasant, pleasant, unpleasant, neutral); image presentation within each block was randomized. Each image was presented once for 1500 ms. For further details regarding the task, see its previous application to examine emotional reactivity (Hill, Lane, & Foti, 2019). The current series of studies limited investigation to resting-state FAA rather than FAA during this emotion task or ERPs also associated with emotional reactivity and regulation, such as the Late Positive Potential, in order to facilitate feasibility of assessment for both adults and infants across Studies 1-3.

Data Recording and Processing

FAA. Continuous EEG was recorded while participants completed the resting-state task using an actiCHamp amplifier (Brain Products GmbH, Munich, Germany). Offline processing was conducted using BrainVision Analyzer software (Brain Products). Data were segmented into 1-second intervals with 50% overlap. Artifact rejection was performed using an automated procedure with maximum allowed voltage steps of 50 μV/ms and maximal allowed difference values of 150 μV per 200-ms interval. A Fast Fourier Transform was then applied to the data with 1-Hz resolution and 50% hamming windows corresponding to 25% taper on each end. FAA was then scored as a computation (log right – log left) of the average activity in the alpha band (8-13 Hz for adults) at a pooling of electrode sides F3 and F7 (left) and F4 and F8 (right). Alpha activity is inversely related to brain activity, and thus greater FAA as calculated in the current study

represents greater relative left frontal brain activity. For a summary of processing procedures, see Figure 2.

HRV. Continuous ECG was recorded while participants completed the resting-state task using either the ActiWave Cardio device (CamNtech Ltd, Cambridge, UK) or Faros monitor (Bittium, Oulu, Finland).[2] Data processing was conducted first using QRSTool (Allen, Chambers, & Towers, 2007) to inspect the inter beat interval data and then using CardioEdit software (Brain-Body Center, Chapel Hill, NC) to remove artifacts, and CardioBatch Plus software (Brain-Body Center, Chapel Hill, NC) to assess high frequency (i.e., respiratory sinus arrhythmia; RSA), low frequency, and the low frequency / high frequency ratio domain measures. CardioBatch Plus derives HRV measures using Porges' method and a polynomial filter to detrend the data (Porges & Bohrer, 1990). In the calculation of RSA, a band-pass filter is also applied to extract the variance due to respiration (.12 - .4 Hz in adults). HRV measures were originally calculated in 30-second epochs, and the average of these epochs across the three-minute resting-state task were used to operationalize LF-HRV and RSA variables. The LF/HF HRV ratio was then calculated by dividing LF-HRV by RSA. Of the 31 mother participants with ECG data, all 30-second epochs were available and used in the calculation of average LF-HRV and RSA. For a summary of processing procedures, see Figure 2.

[2] Analyses were assessed first with the entire dataset and second without the data collected via Faros monitors in order to assess for differences across collection modalities.

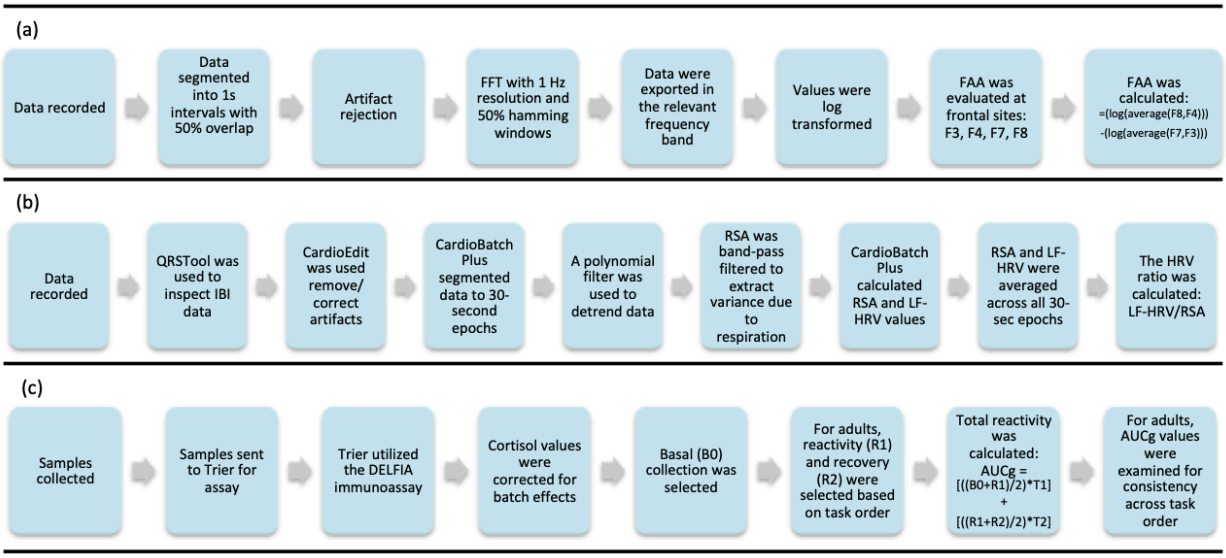

Figure 2. Depiction of processing procedures for FAA (a), HRV (b), and AUCg (c).

Salivary cortisol reactivity (AUCg). While participants performed the lab tasks, salivary cortisol was collected in four stages: two possible basal collections (B0), reactivity (R1), and recovery (R2). For each salivary administration, participants were instructed to place a salivette in their lower lip for approximately one minute. Each sample was systematically administered following published practices (Bernard, Kashy, Levendosky, Bogat, & Lonstein, 2017; Burke et al., 2005; Buss et al., 2003). For adults, two basal administrations were built into the assessment battery: one upon completing the resting-state task in the EEG booth in order to allocate time for getting acquainted with the EEG equipment and booth, and one immediately after completion of the IAPS task. Reactivity collection was administered twenty minutes after the IAPS task, and the recovery collection was administered in the subsequent 20 minutes (i.e., 40 minutes after IAPS task completion). Salimetrics salivettes were used to collect salivary assays, and data were assayed at Universitat Trier in Germany using the DELFIA, a competitive solid phase time-resolved fluorescence immunoassay with flouromeric endpoint detection. Detection limits were 0.17-100 nmol/l. Where possible, samples were analyzed in duplicate and mean cortisol values were provided. Three control samples were used to assess mean and standard deviation values in order to assure quality assay for each plate. The current samples were analyzed across 17 plates. Intra-assay coefficients of variation were kept between 4.0- 6.7% and inter-assay coefficients of variation were kept between 7.1-9.0%.

In order to compute cortisol reactivity from the assayed basal (B0), reactivity (R1), and recovery (R2) collections, a summary measurement was calculated. Specifically, the area under the curve with respect to ground (AUCg) measurement was used to operationalize cortisol reactivity in the current series of studies. AUCg was chosen to calculate cortisol reactivity as it is thought to represent total hormonal output (Fekedulegn et al., 2007) and incorporates both reactivity and recovery while controlling for exact measurement intervals (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Before AUCg calculation, data was corrected for assay batch (e.g., the 17 plates used to assay the cortisol samples)[3] and basal assessment was selected. In the current study, cortisol collected immediately after completing the IAPS task was selected as the basal assessment for calculations, because the two available basal assessments did not significantly

[3] Batch significantly predicted cortisol values across all samples, $R^2 = .01$, $F(1, 434) = 4.63$, $p = .032$.

differ (t (13) = 1.38, p = .190; t (14) = -.53, p = .602), and the immediate post-task collection offered greater time consistency across participants. AUCg was calculated by summing the averages of basal and reactivity values + reactivity and recovery values, each controlling for the relevant time intervals.[4] For a summary of processing procedures, see Figure 2.

In the current study, 17 (60.71%) of participants demonstrated the expected rise in cortisol in response to the IAPS viewing task; however, average cortisol values decreased across collections, B0: M = -.27; R1: M = -.32; R2: M = -.39. These differences were not significant, all p's > .05.

Data Analysis

Prior to performing the following analyses for the specific aims of the project, the data were assessed for normal distributions (e.g., outliers, skewness), and variables matched these criteria unless otherwise noted. Pairwise deletion was used for missing data. This technique is commonly used in efforts to maintain as much data as possible for each analysis without reducing variance in the dataset. Bivariate associations with demographic variables (i.e., age) were assessed and modeled in regression analyses where indicated by bivariate associations. Effect sizes were reported across analyses. Sensitivity analyses were conducted using G*Power software version 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). All data were calculated and evaluated using Microsoft Excel version 14.7.2 (Microsoft Corp., Redmond, WA) and SPSS Statistics version 26 (IBM Corp., Armonk, NY).

Study 1 sought to assess how the coordination, or lack thereof, of regulation across physiological systems relates to depression. Based on the literatures for each physiological indicator and the overarching ECI framework, I hypothesized that scores on the DASS-21 depression scale would be negatively associated with FAA, HRV, and AUCg. For HRV, I predicted negative associations with depression would be strongest for RSA. Bivariate correlations assessed relations amongst all physiological measures (FAA, HRV, and cortisol reactivity) and maternal symptom severity from the depression scale of the DASS-21. Because internalizing symptoms are demonstrably related (Krueger & Markon, 2006; Moffitt et al., 2007), DASS-21 anxiety and stress scores were also included in correlational analyses to investigate the specificity

[4] Because data were collected as part of a larger study, the IAPS task was presented in counterbalanced order with a cognitive task. AUCg values were assessed for consistency across task administration order, (t(26) = .85, p = .402).

of effects with DASS-21 depression. Next, follow-up analyses regressed current maternal DASS-21 depression scores onto maternal FAA, RSA, and AUCg, as simultaneous predictors, to assess the overall variance jointly accounted for by the indicators as well as the unique effects of each physiological indicator.

Sensitivity Analysis

Meta-analyses assessing physiological indicators in relation to depression in adults have identified that these relationships generally have small to large effect sizes [e.g., adult FAA and depression, mean weighted r = .26 (Thibodeau et al., 2006); adult HRV and depression, Hedges' g = -.21 (Kemp et al., 2010); adult cortisol reactivity and depression, d = -1.06 (Burke et al., 2005)]. For bivariate correlational analyses with 35 total mother participants, I was powered at .80 to detect medium effects (i.e., r = |.33|). For multiple regression analyses with 3 predictors and 35 total mother participants, I was powered at .80 to detect large effects for each predictor (i.e., f^2 = |.35|) (Cohen, 1988).[5]

Results

Descriptive Statistics

Sample characteristics are available in Table 1. The sample was homogenous in terms of mother's education level (70.2% with college degree or higher) and marital status (94.6% married). Annual household income ranged from $10,800 - $280,000 (*median* = $60,000). Over half of the sample (51.43%) had a lifetime history of at least one mental health disorder. Of those with a lifetime history of mental disorder, comorbidity was common (number of diagnoses: *range* = 1-4; M = 1.89). Over one-third of the sample met criteria for lifetime history of MDD (35.10%). Descriptive statistics for lifetime MDD diagnosis cases are available in Table 2.

[5] According to Cohen (1988), f^2 reflects the proportion of variance that is uniquely accounted for by each predictor, above and beyond all other predictors in the model. Guidelines regarding interpretation of size are as follows—small: $f^2 \geq .02$, medium: $f^2 \geq .15$, and large: $f^2 \geq .35$.

Table 1. Study 1: Descriptive Statistics

	N	*Mean*	*SD*
Maternal age (years)	35	32.08	4.92
Household income	32	$71,737.81	$48,977.98
DASS-21 Maternal Internalizing Symptoms			
Depression	34	2.53	2.25
Anxiety	34	1.91	2.23
Stress	34	6.12	3.55
		n	*%*
Education Level (*N* = 35)			
Advanced degree		17	48.6
Bachelor's degree		8	22.9
Associate's degree/some college		7	20.0
High school diploma or less		2	5.7
Marital Status (*N* = 35)			
Married		33	94.3
Never married		2	5.7
SCID diagnoses (*N* = 35)	*Lifetime n*	*Current n*	*% Lifetime*
Bipolar I/II	0	0	0
Major Depressive Disorder	13	3	35.10
Persistent Depressive Disorder	5	2	13.5
Psychosis spectrum	1*	1*	2.7
Alcohol use disorder	6	0	16.2
Substance use disorder (other)	1	0	2.7
Panic Disorder	1	0	2.7
Agoraphobia	0	0	0
Social Anxiety Disorder	2	1	5.4
Specific Phobia	0	0	0
Generalized Anxiety Disorder	4	4	10.8
Obsessive Compulsive Disorder	1	0	2.7

Note. *One individual endorsed psychosis related symptomatology on the screener; however, full administration of the module was not conducted.

Table 2. Study 1: Descriptive Statistics for Major Depressive Disorder Diagnoses

	N	*Mean*	*SD*
Total number of MDD episodes	13	4.00	4.40
"99" cases	3		
	Lifetime n	*Current n*	*% Lifetime*
Comorbid presentations	9	5	69.23
Persistent Depressive Disorder	5	2	38.46
Psychosis spectrum	1*	1*	7.70
Alcohol use disorder	2	0	15.40
Substance use disorder (other)	1	0	7.70
Social Anxiety Disorder	2	1	15.40
Generalized Anxiety Disorder	4	4	30.8
Obsessive Compulsive Disorder	1	0	7.70
		n	*%*
Relation of MDD episodes to birth of baby			
Prenatal period		1	7.70
Postnatal period		3	23.10
Unrelated		3	23.10
Not enough information		6	46.20
Use of mood-altering medication			
Prenatal period		1	7.70
Postnatal period		1	7.70
Unrelated to pregnancy/birth		1	7.70
Absent/never taken		1	7.70
Not enough information		9	69.2

Note. The SCID-5 also allows for a "99" designation in the case that MDD episodes are "too numerous or indistinct to count" (First et al., 2015). *One individual endorsed psychosis related symptomatology on the screener; however, full administration of the module was not conducted.

Bivariate Correlations

Based on the literatures for each physiological indicator (i.e., FAA, HRV, and cortisol reactivity) and the overarching ECI framework, I hypothesized that higher DASS-21 depression scores would be associated with reduced FAA, HRV, and AUCg. For HRV, I predicted RSA and depression would demonstrate the strongest association. Table 3 shows correlations amongst all maternal physiological measures and current maternal internalizing psychopathology. Current depression, anxiety, and stress symptoms were all strongly, positively associated, all *r*'s > .55. Looking at HRV measurements, RSA and LF-HRV shared a moderate, positive association, suggesting that parasympathetic and sympathetic activity share a general factor. LF-HRV and the HRV ratio shared a strong, positive association, suggesting that HRV ratio scores are primarily driven by sympathetic activity in this sample. RSA and the HRV ratio shared a small, non-significant association. None of the symptom scores or physiological indicators were related to maternal age.

With regard to the hypothesized associations, depression was not significantly associated with physiological systems across FAA, HRV, or AUCg indicators. Of note, maternal FAA and RSA shared a moderate, positive association. Cortisol reactivity did not share an association with any other physiological indicator.

Regression Analyses

Next, follow-up analyses regressed maternal DASS-21 depression scores onto physiological indicators (FAA, RSA, and AUCg) as simultaneous predictors to assess the overall variance jointly accounted for by the indicators as well as the unique effects of each physiological indicator. Based on the literatures for each physiological indicator and the overarching ECI framework, I hypothesized that DASS-21 depressive symptoms would be associated with blunted environmental engagement demonstrated across physiological measures and that each measure would offer unique information. The regression model is available in Table 4. The overall model did not significantly predict maternal DASS-21 depression symptoms and each physiological indicator shared a small, non-significant association with depression in the opposite direction of hypotheses.

Table 3. Study 1: Correlations

		1	2	3	4	5	6	7	8	9
1.Depression sx	*r*	1								
	p									
	N	34								
2. Anxiety sx	*r*	.67**	1							
	p	.000								
	N	34	34							
3. Stress sx	*r*	.63**	.55**	1						
	p	.000	.001							
	N	34	34	34						
4. FAA	*r*	.14	.13	.12	1					
	p	.440	.482	.522						
	N	33	33	33	34					
5. RSA	*r*	.24	.11	-.10	.41*	1				
	p	.206	.553	.604	.023					
	N	30	30	30	30	31				
6. LF-HRV	*r*	.01	-.15	-.20	.26	.45*	1			
	p	.974	.433	.279	.164	.011				
	N	30	30	30	30	31	31			
7. HRV ratio	*r*	-.13	-.23	-.14	.01	-.16	.81*	1		
	p	.483	.224	.463	.971	.387	.000			
	N	30	30	30	30	31	31	31		
8. AUCg	*r*	-.03	.06	.02	.08	-.08	-.15	-.08	1	
	p	.901	.782	.933	.700	.721	.467	.711		
	N	27	27	27	28	25	25	25	28	

Table 3 continues

	r	.06	-.13	.04	-.15	-.19	-.05	-.04	-.26	1
9. Age	*p*	.730	.454	.816	.385	.316	.803	.839	.19	
	N	34	34	34	34	31	31	31	28	37

Note. *. Correlation is significant at the 0.05 level (2-tailed). Sx = symptoms from the DASS-21 scales. Blue indicates correlations amongst DASS-21 symptom scores, red indicates correlations amongst HRV indicators, and green indicates hypothesized associations amongst symptom scores and physiological indicators.

Table 4. Regression Predicting Current Maternal Depression Symptoms

Outcome: DASS-21 maternal depression symptoms	*B*	*SE (B)*	β	*t*	*p*
Mother FAA	.182	.191	.224	.951	.353
Mother RSA	.069	.236	.069	.291	.774
Mother AUCg	.041	.176	.050	.231	.819
	Overall R^2 *= .07*				.683

Interim Discussion: Study 1

The present study sought to investigate physiological regulatory systems in relation to depressive symptoms in adults according to two competing models: ECI and ACM. Bivariate associations revealed that the internalizing symptoms of the present sample are particularly interrelated. Associations amongst the subscales is to be expected given their conceptual load onto the broad internalizing domain and high comorbidity rate (Krueger & Markon, 2006; Moffitt et al., 2007); however, it is noteworthy that the associations in this sample are higher than previous investigations with young adult and adult clinical samples, *r* range = .46-.55 (Antony, Bieling, Cox, Enns, & Swinson, 1998; Lovibond & Lovibond, 1995; Osman et al., 2012). HRV associations also indicated that RSA and LF-HRV share a moderate association, such that parasympathetic and sympathetic processes are positively associated, and the HRV ratio seems driven by sympathetic activity. This association supports prior work indicating that heart rate processes are complex, and parasympathetic and sympathetic processes should not be considered orthogonal; moreover, this association may reflect that both the low frequency and high frequency heart rate are affected by breathing patterns (Shaffer & Ginsberg, 2017). Of note, maternal FAA and RSA shared a moderate, positive association, suggesting broad coordination across neural and autonomic indices of approach motivation and flexibility to environmental demands. Cortisol reactivity did not share an association with any other physiological indicator, suggesting that AUCg to a specific stressor may not capture the same conceptual mechanism as resting-state FAA and HRV.

Current depressive symptoms did not significantly relate to any physiological indicator. These findings are inconsistent with FAA, HRV, and cortisol reactivity literatures broadly, and there are several plausible explanations for these results. First, while meta-analyses suggest the

robust nature of associations across FAA, HRV, cortisol reactivity, and depression (Burke et al., 2005; Kemp et al., 2010; Thibodeau et al., 2006), each of these literatures also offer research into the nuance of these associations. For example, several studies have demonstrated that comorbid anxiety dampens associations between depression and FAA (Bruder et al., 1997; Kentgen et al., 2000; Thibodeau et al., 2006). Second, research investigating reliability and current symptom status have found that reduced FAA and RSA relate to lifetime history of depression as indicated by diagnosis rather than current symptom severity (Allen & Reznik, 2015; Allen, Urry, Hitt, & Coan, 2004; Kemp et al., 2010; Nusslock et al., 2011; Urry, Hitt, & Allen, 1999). Third, much of the prior work on psychophysiological indices and depression have recruited diagnostically specific samples; that is, individuals that meet criteria for MDD without comorbid diagnoses. This is not true of the current sample, wherein over half of participants met criteria for one lifetime diagnosis of a mental disorder and over two-thirds of MDD cases met criteria for at least one comorbid disorder.

It is important to note that while a majority of research investigating psychophysiological indicators in depression have employed both male and female adults, the current findings are also discrepant with research investigating these associations in women-only samples—which have found blunted FAA in depressed mothers with young children (Diego, Field, & Hernandez-Reif, 2001), blunted HRV in pregnant women with depression (Shea et al., 2008), and blunted cortisol reactivity in women with remitted MDD when compared to women without history of MDD (Bagley, Weaver, & Buchanan, 2011). Given the substantial amount of comorbidity in the present sample, results suggest blunted physiological regulation may be most related to "pure" depression. Further investigation of these physiological indicators within the context of maternal symptomatology—that is, depression with and without comorbid presentations—is essential to understanding how physiological regulatory styles are related to vulnerability for depression in adult women.

STUDY 2

Blunted physiological flexibility may extend beyond markers of current depression in adults to also capture markers of risk early in the lifespan—particularly for offspring of mothers with depression. As early as infancy, the physiological pattern of depression risk (i.e., risk based on maternal symptomatology; Goodman, 2007) is broadly similar to the pattern of depression in adults, including dysregulation in neural, HPA, and autonomic systems (Allister, Lester, Carr, & Liu, 2001; Diego et al., 2004; Fernald et al., 2008; Jones et al., 1998; Yaroslavsky et al., 2014). Specifically, fetuses of mothers with depression present blunted and delayed responses to environmental changes, as measured by heart rate (Allister et al., 2001), and withdrawal RSA patterns in childhood predict increasing depressive symptoms in adolescence (Yaroslavsky et al., 2014). Offspring of mothers with depression have blunted FAA in comparison to those of mothers without depression as young as newborns, and increased psychopathology symptoms later in childhood (Diego et al., 2004; Field, Fox, Pickens, & Nawrocki, 1995; Jones et al., 1998; Peltola et al., 2014; Soe et al., 2016; Thibodeau et al., 2006). Additionally, one previous study demonstrated that blunted FAA was associated with higher basal and reactivity cortisol levels for six-month old infants (Buss et al., 2003). Notably, cortisol reactivity seems to be potentiated in newborns of mothers with depression and this pattern seems to reverse by toddler years, such that salivary cortisol of children (age range: 2.5-6 years) with depressed mothers exhibit blunted baseline and reactivity cortisol levels (Diego et al., 2004; Fernald et al., 2008).

Research across neural, HPA, and autonomic systems broadly suggests that offspring of mothers' with depression seem to demonstrate blunted environmental responsiveness according to one-to-one analyses; however, these relationships are less clear specifically for infants aged 12-months, as described studies include offspring across developmental ranges from in utero to later childhood. Twelve-month-olds present a particularly opportune developmental window for investigating these questions, as previous work has demonstrated that RSA relates to approach motivation and developmental status at this age (Richards & Cameron, 1989), frequency shifts in brain maturation stabilize at this age, which facilitates FAA assessment (Marshall, Bar-Haim, & Fox, 2002), and stress reactivity, particularly when measured by AUCg, is reliable across time and psychological stressors at this age (Goldberg et al., 2003). In addition, as with Study 1, utilizing indicators of multiple physiological systems within one sample is needed to inform theoretical

underpinnings of environmental responsiveness in infants of mothers with depressive symptomatology. Broad blunting of physiological indicators across response systems in infants of mothers with depression would support ECI; however, discordant blunting across the responses systems of infants with higher levels of maternal depression would support the ACM. Moreover, it is unclear which physiological indicator in infants shares the strongest relationship with maternal depression, or if these indicators share overlapping effects with maternal depression.

The aim of the current study was to replicate results found in previous research utilizing FAA, HRV, and salivary cortisol reactivity assessments across a range of developmental stages specifically in 12-month infants to comparatively assess relationships between each of these systems and maternal depression. Capturing patterns of physiological differences between infants of mothers with and without depression symptoms, within a particular window of development, will assist in elucidating associations between adult depressive symptomatology and infant risk for development of symptoms. In order to replicate previous research demonstrating that maternal depression is related to physiological indicators in infants, bivariate correlations first assessed relationships amongst current maternal depression scores and all infant physiological measures. After the bivariate correlations, current maternal depression scores were regressed onto infant physiological indicators as simultaneous predictors to (1) assess the joint variance captured by the indicators in relation to maternal depression and (2) assess the unique effects of indicators above and beyond the others. Based on the literatures for each physiological indicator in infants of mothers with depression and the overarching ECI framework, I hypothesized that maternal depression would be associated with overall blunted reactivity in infants across the physiological measures (FAA, HRV, and AUCg) and that each of these indicators would offer unique information.

Method

Participants

As described in Study 1, the current sample was recruited from Dr. Kelleher's Infant Development Study. Specific to Study 2, infants (of the mothers described in Study 1) aged 12 months +/- 1 month were recruited from this sample without any additional burden on participants.

Of the 35 infants whose mothers participated in laboratory tasks and clinical assessment, one infant's EEG data was excluded from analysis for significant EEG artifact (i.e., > 90% rejection), one infant's ECG data was lost due to equipment failure, and eleven infants' cortisol data was lost primarily due to declined or insufficient saliva collection across reactivity administrations. Thus, of the 35 infants, 97.1% of FAA (n = 34), 97.1% of HRV (n = 34), and 68.6% of cortisol reactivity (n = 24) values were available for analyses; 21 infant participants had complete psychophysiological data. Participation was voluntary, and infants' mothers were compensated for participation. The Purdue University Institutional Review Board formally approved this research.

Inclusion/Exclusion Criteria

To determine study eligibility, infants were screened and excluded if born prematurely (i.e., < 37 weeks gestation), had a major surgery, major illness, or birth trauma, had professionally reported developmental concerns, or had an immediate family member with autism spectrum disorder or intellectual disability. After participation, infant data were excluded if a developmental delay was identified by developmental assessments discussed below. Specifically, infants 2 standard deviations below the sample mean in overall level of adaptive functioning on the Adaptive Behavior Composite or Early Learning Composite[6] would be excluded from data analysis. All infants were within this threshold and thus included in analyses.

Procedures

Relevant to the current series of studies, the infant developmental assessments and interview with the mother took approximately 1.5 hours. The physiological recording sessions took approximately 1 hour.

[6] In one case, the MSEL and Vineland-3 measures were not completed due to time constraints. This participant did complete the Bayley-III (Bayley, 2006), however, and this developmental measure was used to assess adaptive functioning.

Developmental Assessment

Vineland Adaptive Behavior Scales, Third Edition (Vineland-3). The Vineland-3 (Sparrow, Balla, Cicchetti, Harrison, & Doll, 1984) is a parent interview that assesses a range of functional behaviors across 3 domains (Communication, Daily Living Skills, and Socialization) and forms a composite termed the overall Adaptive Behavior Composite and offers standardized scores based on age-matched peers. Clinical psychology graduate students and lab staff, trained in the administration, scoring, and interpretation of this measure, administered all Vineland-3 interviews.

Mullen Scales of Early Learning (MSEL). The MSEL (Mullen, 1995) is a play-based developmental assessment for cognitive functioning. The MSEL assesses a collection of related but distinct cognitive skills across 5 domains (Gross Motor, Visual Reception, Fine Motor, Receptive Language, and Expressive Language) and utilizes these scales to provide an overall Early Learning Composite and offers standardized scores based on age-matched peers. Clinical psychology graduate students and lab staff, trained in the administration, scoring, and interpretation of this measure, administered all MSEL assessments.

Physiological Assessment: Infant Laboratory Tasks

Infant participants completed the resting-state task described in Study 1 while continuous EEG and ECG were recorded. Infants completed the resting-state task in a separate session, on separate days from their mothers. As with mothers, infant participants were not instructed to close their eyes to increase feasibility of conducting this task with infants. Infants sat in their mothers' laps during the task.

In lieu of the emotionally evocative IAPS task, infants completed the Lab-TAB arm restraint task to assess cortisol reactivity (Goldsmith & Rothbart, 1996). In this task, a novel toy was offered to the infant, and the mother and infant played with the toy for 30 seconds. Then, the mother restrained the infant's arms to his/her side so that the infant could see, but not touch, the toy for 30 seconds. Afterward, the mother was instructed to tell the infant that she was "just teasing" and she and the infant played with the toy once again. Clinical psychology graduate students and lab staff trained in the administration of this task guided mother participants through each step. This task is considered to be a psychological stressor as it elicits frustration and anger from the

infant, and it has been used previously to elicit an increased salivary cortisol response in twelve-month-old infants (Bernard et al., 2017).

Data Recording and Processing

Physiological recording and processing procedures were equivalent to those described in Study 1, with the following qualifications for infant assessment:

FAA. Frontal alpha asymmetry was scored in the alpha band for infants (6-9 Hz) rather than the alpha band for adults (8-13 Hz) (Marshall et al., 2002).

HRV. In the calculation of RSA, the band-pass filter applied to extract the variance due to respiration was tied to the respiration frequency for infants (.3 – 1.3 Hz). Of the 34 infant participants with available ECG data, all 30-seconds epochs were available and went into the calculation of average RSA and LF-HRV values.

AUCg. For infants, two basal collections were compared to assess baseline cortisol: one administered approximately twenty minutes upon first arrival to the lab, before lab tasks began, in order to allocate time for getting acquainted with the room and going through consent procedures with the mother. The second basal collection was administered immediately after completion of the Lab-TAB reactivity press. Reactivity collection was administered twenty minutes after the Lab-TAB arm restraint task (Bernard et al., 2017; Goldsmith & Rothbart, 1996), and recovery was administered in the subsequent twenty minutes (e.g., forty minutes after completion of the task). As in Study 1, cortisol collected immediately after completing the task was selected as the basal assessment for calculations. In this case, the post-task basal administration was selected because it was significantly lower than the basal collected at arrival, $t(23) = 2.15$, $p = .042$, $d = .44$.

In the current study, 17 (70.83%) of infant participants demonstrated the expected rise in cortisol in response to the Lab-TAB arm restraint task. Average cortisol values were significantly higher from B0 ($M = .15$) to R1 ($M = .29$; t (23) -2.31, $p = .030$, $d = .46$); and did not differ across B0 and R2 ($M = .11$) collections, t (23) = .21, $p = .836$, $d = .04$.

Data Analysis

Data reduction procedures were equivalent to those described in Study 1. Bivariate associations with demographic variables (i.e., age and sex) were assessed and modeled in regression analyses where indicated by bivariate associations. Effect sizes were reported across analyses. Sensitivity analyses were conducted using G*Power software version 3.1 (Faul et al., 2009). All data were calculated and evaluated using Microsoft Excel version 14.7.2 (Microsoft Corp., Redmond, WA) and SPSS Statistics version 26 (IBM Corp., Armonk, NY).

Study 2 sought to assess the relationship between regulation across infant physiological systems and maternal DASS-21 depressive symptoms. Based on the literatures for each physiological indicator in infants of mothers with depression and the overarching ECI framework, I hypothesized that maternal DASS-21 depression would be associated with overall blunted regulation in infants across FAA, HRV, and AUCg. In order to replicate previous research demonstrating that maternal depression is related to physiological indicators in infants, bivariate correlations first assessed relationships amongst maternal depression symptom severity from the depression scale of the DASS-21 and infant FAA, HRV, and AUCg. Because internalizing symptoms are demonstrably related (Krueger & Markon, 2006; Moffitt et al., 2007), maternal DASS-21 anxiety and stress scores were also included in correlational analyses to investigate the specificity of effects with DASS-21 depression. After the bivariate correlations, maternal DASS-21 depression scores were regressed onto infant FAA, HRV, and AUCg as simultaneous predictors in order to (1) assess the joint variance captured by the indicators in relation to maternal depression and (2) assess the unique effects of indicators above and beyond the others.

Sensitivity Analysis

Previous studies assessing infant physiological indicators in relation to maternal depression have identified that these relationships generally have small to medium effect sizes [e.g., infant RSA and maternal depression, r = .18 (Gueron-Sela et al., 2016), infant FAA and maternal depression, mean weighted r = .32 (Thibodeau et al., 2006); infant cortisol reactivity and maternal depression, β = .29 (Feldman et al., 2009)]. For bivariate analyses with 35 dyad pairs (35 mothers, 35 infants), this study was powered at .80 to detect medium effects (i.e., r = |.33|). For multiple

regression analyses with 3 predictors and 35 dyads, the analysis was powered at .80 to detect large effects for each predictor (i.e., $f^2 = |.35|$).

Results

Descriptive Statistics

Sample characteristics are available in Table 5. The sample was homogenous in terms of infant race and ethnicity (89.2% non-Hispanic white). All infants met inclusion criteria based on developmental assessments.

Table 5. Study 2: Descriptive Statistics

	N	*Mean*	*SD*
Infant age (months)	35	12.22	.88
Early Learning Composite	35	95.82	10.39
Adaptive Behavior Composite	35	102.53	12.11
		n	*%*
Infant sex			
Male		18	51.4
Female		17	48.6
Infant race/ethnicity			
White		33	91.4
Multiple		3	8.6
Hispanic/Latinx		0	0

Note. The Early Learning Composite is derived from the Mullen Scales of Early Learning. The Adaptive Behavior Composite is derived from the Vineland-3.

Bivariate Correlations

Based on the literatures for each physiological indicator (i.e., FAA, HRV, and cortisol reactivity) and the overarching ECI framework, I hypothesized that maternal DASS-21 depressive symptoms would be associated with blunted environmental engagement in infants, demonstrated across physiological domains. Table 6 shows correlations amongst all infant physiological measures and current maternal internalizing psychopathology across DASS-21 scales. For infant HRV measurements, RSA and LF-HRV shared a moderate, positive association, suggesting that parasympathetic and sympathetic activity share a general factor. Infant LF-HRV and the HRV ratio shared a strong, positive association, suggesting that HRV ratio scores are primarily driven by sympathetic activity. RSA and the HRV ratio shared a moderate, non-significant, and negative association, further supporting that the HRV ratio is driven by sympathetic activity. None of the maternal DASS-21 symptom scores or infant physiological indicators were related to infant age or sex.

With regard to the hypothesized associations, maternal DASS-21 depression shared a small, non-significant negative association with infant FAA; a moderate, non-significant negative association with infant LF-HRV; a moderate, significant negative association with the infant HRV ratio, and a small, non-significant positive association with infant AUCg; maternal DASS-21 depression and infant RSA did not share an association. Together, these results suggest that maternal depression is most strongly associated with infant autonomic dysregulation, and that HRV associations may be driven by decreased sympathetic activity.

Table 6. Study 2: Correlations

			1	2	3	4	5	6	7	8	9
1.	Maternal depression sx	*r*	1								
		p									
		N	34								
2.	Maternal anxiety sx	*r*	.67**	1							
		p	.000								
		N	34	34							
3.	Maternal stress sx	*r*	.63**	.55**	1						
		p	.000	.001							
		N	34	34	34						
4.	Infant FAA	*r*	-.10	.16	-.13	1					
		p	.581	.367	.476						
		N	33	33	33	34					
5.	Infant RSA	*r*	.03	.06	-.19	-.26	1				
		p	.892	.762	.286	.151					
		N	33	33	33	33	34				
6.	Infant LF-HRV	*r*	-.34	-.25	-.21	-.21	.48*	1			
		p	.052	.153	.243	.233	.005				
		N	33	33	33	33	34	34			
7.	Infant HRV Ratio	*r*	-.37*	-.29	-.07	.04	-.32	.67*	1		
		p	.036	.107	.687	.809	.07	.000			
		N	33	33	33	33	34	34	34		
8.	Infant AUCg	*r*	.20	.17	.05	.05	-.02	-.02	-.05	1	
		p	.360	.433	.824	.839	.939	.945	.806		
		N	23	23	23	23	24	24	24	24	

Table 6 continues

		1	2	3	4	5	6	7	8	9
9. Infant age	*r*	-.08	-.03	.09	-.01	.00	.09	-.14	.16	1
	p	.645	.882	.623	.941	.988	.630	.415	.467	
	N	34	34	34	34	34	34	34	24	35
10. Infant sex	*r*	-.05	-.04	.14	-.03	-.30	-.14	-.17	.01	.07
	p	.765	.822	.448	.872	.090	.432	.345	.963	.710
	N	34	34	34	34	34	34	34	24	35

Note. * Correlation is significant at the 0.05 level (2-tailed). Sx = symptoms from the DASS-21 scales. Blue indicates correlations amongst DASS-21 symptom scores, red indicates correlations amongst HRV indicators, and green indicates hypothesized associations amongst maternal symptom scores and infant physiological indicators.

Regression Analyses

Next, follow-up analyses regressed maternal DASS-21 depression scores onto infant FAA, HRV, and AUCg to assess the overall variance jointly accounted for by the indicators as well as the interplay of physiological indicators. Based on the literatures for each physiological indicator (i.e., FAA, HRV, and cortisol reactivity) and the overarching ECI framework, I hypothesized that maternal DASS-21 depressive symptoms would be associated with blunted environmental engagement in infants, as demonstrated across physiological measures. In the regression analyses, HRV was initially operationalized specifically as RSA, as RSA and depression history have the largest effect in the literature (Kemp et al., 2010). The regression model is available in Table 7. Infant FAA, RSA, and AUCg did not significantly predict maternal DASS-21 depression symptoms.

Table 7. Regression Predicting Current Maternal Depression Symptoms

Outcome: Maternal DASS-21 depression symptoms	*B*	*SE (B)*	β	*t*	*p*
Infant FAA	.00	.19	.00	.00	.999
Infant RSA	.19	.21	.20	.90	.380
Infant Cortisol reactivity	.16	.18	.19	.85	.409
	Overall R^2 = .08				.679
Outcome: Maternal DASS-21 depression symptoms	*B*	*SE (B)*	β	*t*	*p*
Infant FAA	-.10	.17	-.12	-.59	.565
Infant LF-HRV	-.46	.18	-.51	-2.51	.022
Infant Cortisol reactivity	.17	.16	.21	1.06	.301
	Overall R^2 = .29				.101

Because infant LF-HRV was moderately associated with current maternal depression in correlational analyses, an additional regression model was ran such that HRV was operationalized as LF-HRV rather than RSA. The overall model remained non-significant; however, infant LF-HRV shared a significant moderate, negative association with maternal DASS-21 depression, such that infant LF-HRV shares a strong association with current maternal depression symptoms while controlling for other infant physiological indices. In this model, FAA also shared a negative, though small and non-significant, association with maternal DASS-21 depression symptoms. Cortisol reactivity shared a positive, though small and non-significant, association with maternal DASS-21 depression symptoms. Together, these results again suggest that maternal depression is most strongly associated with infant sympathetic dysregulation.

Interim Discussion: Study 2

The present study sought to investigate infant physiological regulatory systems in relation to maternal depressive symptoms according to two competing models: ECI and ACM. Bivariate associations revealed that HRV associations in infants paralleled those demonstrated in adults—that RSA and LF-HRV share a moderate association, such that parasympathetic and sympathetic processes are positively associated, and the HRV ratio seems driven by sympathetic activity. Current maternal depressive symptoms related to blunted infant LF-HRV, as hypothesized. Current maternal depressive symptoms also related to blunted FAA as hypothesized, though this association was small and non-significant. However, infant RSA was not associated with maternal depression symptoms, and cortisol reactivity shared a small, positive association, both contrary to hypotheses.

Across the pattern of effects, these results lend primary support for the ACM model, as infant patterns varied in relation to maternal depression across physiological systems; however, a majority of effects were small and non-significant. These findings are inconsistent with the maternal depression and infant FAA, HRV, and cortisol reactivity literatures broadly, and there are several plausible explanations for these results. First, timing of maternal symptoms and assessment each may play a role in these associations. Research conducted by Diego and colleagues (2004) suggests that the associations between maternal depression and infant physiological indicators are strongest when maternal depression occurs during the prepartum period of pregnancy. Available data suggests that only 7.70% of the current MDD sample

experienced a depressive episode in the prepartum period. Moreover, the meta-analysis by Thibodeau and colleagues (2006) demonstrated that the association between maternal depression and infant FAA is larger the younger the infant is at time of assessment. It is possible that effect sizes reduce as other factors also contribute to infants' development, such as maternal current psychosocial functioning or parenting style. Second, just as in Study 1, comorbid disorder presentation, particularly comorbid anxiety, in the current sample of mothers may have led to reduced associations. Indeed, previous work investigating transmission of depression risk has found that family history of anxiety blunts associations between maternal depression and infant neurophysiological indices of depressive risk (Kujawa, Hajcack Proudfit, & Klein, 2016).

The pattern of effects demonstrated here between maternal depression and infant physiological regulation is divergent from the pattern between maternal depression and physiological regulation demonstrated in Study 1. Although a majority of effects were small and non-significant, these divergent patterns may suggest that current depression symptoms in mothers affects infant physiological regulation, particularly sympathetic regulation as measured by LF-HRV, to a greater extent than it affects their own physiological regulation. One explanation for this difference can be found in the difference between current depressive symptoms and lifetime history of MDD in adult physiological patterns. As reviewed in Study 1, previous research has demonstrated that, in adults, reduced FAA and RSA relate to lifetime history of MDD rather than current symptom severity (Allen & Reznik, 2015; Allen, Urry, Hitt, & Coan, 2004; Kemp et al., 2010; Nusslock et al., 2011; Urry, Hitt, & Allen, 1999). However, for offspring neurophysiological functioning, subclinical levels of maternal depression during pregnancy have been demonstrated to prospectively predict blunted FAA in newborns (Gustafsson, Grieve, Werner, Desai, & Monk, 2018). Current maternal psychosocial functioning may be particularly important in assessing impacts on infant physiological regulation—for example, the effect between maternal depression and infant FAA is strongest in infants who spend at least 50% of waking time with their mothers, suggesting that conditional effects play a role. One such conditional effect may be parenting style, which is impacted by current maternal psychosocial functioning and is associated with further reduced infant FAA across infants with depressed mothers (Diego, Field, Jones, & Hernandez-Reif, 2006; Wen et al., 2017). Moreover, heightened scores across domains on the DASS-21 may be more indicative of current life distress in adults than lifetime MDD, and maternal stress may then affect physiological regulation in infants. Indeed, previous work has suggested that

heightened maternal cortisol reactivity in pregnancy, reflective of current stress, prospectively predicts blunted HRV in infants (Rash, Campbell, Letourneau, & Giesbrecht, 2015). Together, results across Studies 1 and 2 emphasize the need for further investigation of the associations amongst mother and infant physiological regulatory patterns to better identify markers of vulnerability to depression across the lifespan.

STUDY 3

As described across Studies 1 and 2, the literature suggests that depression is related to blunted environmental responsiveness in both mothers with depression and their offspring. However, research directly assessing the relationships between mother and infant physiological reactivity across neural, HPA, and autonomic systems, and the role of depression in these associations, are current gaps in the literature. Though these associations are seldom examined, one study in a healthy sample suggests HPA activity as assessed by salivary cortisol reactivity is highly related between mothers and infants (Feldman et al., 2009). Additionally, one study in mothers and their children (aged 7-11 years) suggests that autonomic activity, as assessed by RSA, within specific interactions is discordant (i.e., negatively associated) within dyads with maternal depression (Woody, Feurer, Sosoo, Hastings, & Gibb, 2016).

Research assessing the associations of multi-system physiological regulation in mothers and infants is critical to facilitate assessment for depression vulnerability across the lifespan. Capturing vulnerability for depression in infants at high risk will offer mechanisms for creation of more accurate, accessible assessments of depression risk early in the lifespan—before symptom onset. Thus, the central aim of the current study was to examine the physiological associations between mothers and infants across neural, autonomic, and HPA domains. Understanding the intergenerational transmission of physiological regulation would offer candidate indices for detection of prospective risk in infants. Further, understanding a profile of physiological regulation indices indicative of prospective risk would lead to a sum of these effects, cumulatively providing greater clinical significance. The development of depression is characterized by high equifinality and heterogeneity (Sullivan, Neale, Kendler, 2000), making prediction of risk and onset difficult. However, demonstrated markers of vulnerability— specifically FAA, HRV, cortisol reactivity, and the interplay across these physiological systems—may share stronger familial associations due to higher specificity.

Capturing the relationships of physiological flexibility across various systems between infants and mothers will provide non-abstract, mechanistic indicators of potential depression risk, laying the foundation for future work to identify prospective onset risk. Study 3 sought to assess intergenerational associations of physiological indicators related to depression to determine whether patterns across indicators can be used to identify early markers of risk. Additionally, there

are competing theoretical models regarding the role of depression in mother-infant associations. First, if intergenerational transmission of depression risk is captured via intergenerational transmission of physiological regulatory indices, the presence of maternal depression should not moderate dyadic associations. However, one line of current research suggests that maternal depression may dampen physiological concordance. Specifically, Skoranski and colleagues (2017) found that RSA associations between mother and toddler were lower when maternal engagement was also low, behavior that has been previously associated with maternal depression over time (Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Letourneau et al., 2012; Skoranski, Lunkenheimer, & Lucas-Thompson, 2017). In the present study, correlational analyses were used to assess the associations between mother and infant for each physiological indicator. Subsequently, regression analyses were utilized to assess the moderation effects of depression on the association between mothers' and infants' physiological indicators. Based on the literature regarding maternal depression affecting offspring physiology and the limited work assessing physiological concordance, I hypothesized that (a) physiological indicators would be related across mother and infant and that (b) maternal depression would moderate the association between mother and infant physiology.

Method

Participants

Participants in Study 3 were the mother and infant dyadic pairs described in Studies 1 and 2.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were equivalent to those described in Studies 1 and 2 for mothers and infants, respectively.

Procedures, Assessment, Data Recording and Processing

Procedures, Clinical, developmental, and physiological assessments, and data recording and processing were equivalent to those described in Studies 1 and 2. See Figures 1 and 2 for reference.

Data Analysis

Data reduction procedures were equivalent to those described in Studies 1 and 2. Study 3 sought to assess intergenerational associations of physiological indicators related to depression in order to examine whether patterns across indicators could be used to identify early markers of depression vulnerability. Based on the literature regarding maternal depression affecting offspring physiology, I hypothesized that physiological indicators would be related across mother and infant. Additionally, due to the competing theoretical models regarding the role of depression in mother-infant associations, I predicted that maternal DASS-21 depression may moderate intergenerational associations across physiological systems. Correlational analyses were used to assess the associations between mother and infant for FAA, HRV, and AUCg indices. Subsequently, regression techniques were utilized to assess the moderation effects of maternal DASS-21 depression on the association between mothers' and infants' physiological indicators. Specifically, four models were constructed to investigate FAA, RSA, LF-HRV, and AUCg. In each model, the infant's physiology (e.g., FAA) was regressed onto maternal physiology (e.g., FAA), current maternal DASS-21 depression, and the interaction of maternal physiology with maternal DASS-21 depression (e.g., FAA*maternal depression). Each variable was standardized before creating the interaction term.

Sensitivity Analysis

Few previous studies have assessed the relation between mother and infant physiological indicators. One study assessing cortisol reactivity demonstrated that mother and infant share a moderate association, $r = .42$; (Feldman et al., 2009). For correlational analyses with 35 dyad pairs, this study was powered at .80 to detect medium effects (i.e., $r = |.33|$). For regression analyses with 4 predictors and 35 dyad pairs, the analysis was powered at .80 to detect large effects for each predictor (i.e., $f^2 = |.40|$).

Results

Bivariate Correlations

Based on the literature regarding maternal depression affecting offspring physiology and the limited physiological concordance literature, I hypothesized that (a) physiological indicators would be related across mother and infant and that (b) maternal depression may blunt the relation between mother and infant physiology. Correlational analyses were used to assess the relationships between mother and infant for each physiological indicator. Table 8 shows correlations amongst all infant and mother physiological measures. Infant FAA and maternal FAA shared a moderate and positive, though non-significant association. Infant RSA and maternal RSA also shared a moderate and positive, though non-significant association, as did the HRV ratio. Infant and mother LF-HRV shared a significant, positive association that was moderately sized. AUCg across infants and mothers shared a non-significant small, negative association.

Regression Analyses

Subsequently, regression analyses were utilized to assess the joint effects of maternal DASS-21 depression and maternal physiological indicators in predicting infant physiology. The regression models are available in Table 9. Because both RSA and LF-HRV measures of HRV were moderately associated between mothers and infants in correlational analyses, the regression models were ran such that HRV was operationalized first with RSA and then with LF-HRV, resulting in 4 total regression models.

For FAA, mother and infant FAA shared a moderate, positive association, and current maternal depression shared a small, negative association with infant FAA. Although each of these associations was non-significant, both effects were in the predicted direction. Furthermore, there was not support for current maternal depression moderating the mother-infant FAA association.

Table 8. Study 3: Correlations

			1	2	3	4	5	6	7	8
1.	Infant FAA	*r*	1							
		p								
		N	35							
2.	Infant RSA	*r*	-.25	1						
		p	.148							
		N	34	35						
3.	Infant LF-HRV	*r*	-.20	.47**	1					
		p	.252	.004						
		N	34	35	35					
4.	Infant HRV ratio	*r*	.04	-.32	.67*	1				
		p	.809	.070	.000					
		N	34	35	35	35				
5.	Infant AUCg	*r*	.04	-.02	-.02	-.05	1			
		p	.840	.937	.935	.799				
		N	24	25	25	25	26			
6.	Mother FAA	*r*	. 30	.18	.01	.05	.05	1		
		p	.093	.319	.964	.801	.824			
		N	33	33	33	33	24	34		
7.	Mother RSA	*r*	-.17	.32	.06	.03	.11	.41*	1	
		p	.376	.081	.771	.877	.643	.023		
		N	30	30	30	30	21	30	31	
8.	Mother LF-HRV	*r*	-.18	.31	.39*	-.11	-.14	.26	.45*	1
		p	.330	.099	.034	.557	.553	.164	.011	
		N	30	30	30	30	21	30	31	31

Table 8 continues

		1	2	3	4	5	6	7	8
9. Mother HRV ratio	*r*	-.08	.12	.38*	.32	-.22	.01	-.16	.81*
	p	.658	.539	.037	.083	.334	.971	.387	.000
	N	30	30	30	30	21	30	31	31
10. Mother AUCg	*r*	-.02	-.05	.16	-.23	-.13	.08	-.08	-.15
	p	.910	.796	.435	.251	.597	.700	.721	.467
	N	27	27	27	27	19	28	25	25

Note. *. Correlation is significant at the 0.05 level (2-tailed). Blue indicates hypothesized correlations between mother and infant FAA, red indicates hypothesized correlations amongst HRV indicators, and green indicates hypothesized associations between mother and infant cortisol reactivity.

Table 9. Regressions Predicting Infant Physiological Measures

Outcome: Infant FAA	*B*	*SE (B)*	β	*t*	*p*
Mother FAA	.27	.15	.32	1.79	.084
Maternal DASS-21 depression	-.19	.20	-.17	-.91	.372
Mother FAA * DASS-21 depression	.02	.17	.02	.12	.902
	Overall R^2 = .11				.331
Outcome: Infant RSA	*B*	*SE (B)*	β	*t*	*p*
Mother RSA	.33	.21	.31	1.54	.137
Maternal DASS-21 depression	-.07	.28	-.05	-.25	.802
Mother RSA * DASS-21 depression	-.14	.33	-.08	-.43	.674
	Overall R^2 = .12				.376
Outcome: Infant LF-HRV	*B*	*SE (B)*	β	*t*	*p*
Mother LF-HRV	.37	.18	.37	2.08	.048
Maternal DASS-21 depression	-.49	.23	-.36	-2.18	.039
Mother LF-HRV * DASS-21 depression	-.19	.24	0.14	-.79	.438
	Overall R^2 = .32				.021
Outcome: Infant AUCg	*B*	*SE (B)*	β	*t*	*p*
Mother AUCg	-.13	.22	-.16	-.58	.569
Current maternal depression	.18	.26	.18	.68	.509
Mother AUCg * DASS-21 depression	-.18	.30	-.16	-.61	.553
	Overall R^2 = .08				.767

For HRV, models utilizing both RSA and LF-HRV demonstrated analogous results. First, mother and infant RSA shared a moderate, positive association; as did mother and infant LF-HRV. However, only the LF-HRV association was significant. Maternal DASS-21 depression was also associated with blunted HRV across models; however, this association was considerably larger for LF-HRV than for RSA. Specifically, maternal DASS-21 depression symptoms and infant LF-HRV shared a moderate and statistically significant, negative association. As with FAA, there was not support for maternal DASS-21 depression moderating the mother-infant HRV associations.

The pattern seen in the AUCg regression model varied from the patterns seen in the FAA and HRV models. Mother and infant AUCg shared a small, negative association and maternal DASS-21 depression was positively associated with infant AUCg—though each of these associations was small and not statistically significant. As with the other models, there was not evidence of DASS-21 depression moderating mother and infant AUCg associations.

Interim Discussion: Study 3

The present study sought to investigate the associations amongst mothers' and infants' physiological regulatory systems in relation to current maternal depressive symptoms. Bivariate associations revealed that neural and autonomic systems shared moderate dyadic associations in the hypothesized direction, though only the association between mother and infant LF-HRV was significant. Mother and infant cortisol reactivity shared a small and non-significant association, in the opposite direction of hypotheses. Neural and autonomic regulation in infants was negatively associated with current maternal depressive symptoms as hypothesized, though effects were small and non-significant. Across all physiological indicators, there was not support for current maternal depression symptoms moderating the associations across mother and infant physiological indices.

The null effects of depression symptoms moderating the associations between mother and infant physiological regulation is in contrast to previous research demonstrating that maternal depression dampens physiological concordance in mother-offspring dyads (Skoranski et al., 2017; Woody et al., 2016). In contrast to the current study of mothers and 12-month-old infants, each of the previous studies were conducted in older children (i.e., 3 years old, 7-11 years old). Age may be a key player in assessing dyadic concordance, as one study also in children (average age = 9.10) demonstrated lack of evidence for FAA dyadic concordance (Wang, Mai, Han, Hu, & Lei, 2018) and the meta-analysis conducted by Thibodeau and colleagues (2006) found that offspring age

significantly effected the strength of maternal depression and infant FAA associations (Thibodeau et al., 2006). However, a more recent meta-analysis of the FAA and maternal depression literature conducted by Peltola and colleagues (2014) did not find evidence of age effects (Peltola et al., 2014). Perhaps then the most meaningful difference between the previous and current studies is the measure of state concordance versus trait associations. Each of the previous studies demonstrated that maternal depression may lead to a break down in moment-to-moment dyadic concordance across a specific lab task; however, the current study measured each physiological indicator separately for mother and infant, on separate days. Thus, the current study is likely measuring the association of more trait-like markers—especially for FAA and HRV, where collection occurred during a resting-state task—while the previous studies were interested in state changes. The current results of moderate trait dyadic associations, which are not moderated by maternal depression, fit well with the theoretical model that intergenerational transmission of physiological regulation may capture a specific pathway to increased depression vulnerability.

Looking at the size and pattern of effects, as each physiological indicator relates across mothers and infants and maternal depression does not blunt this association, preliminary support for intergenerational transmission of depression risk is supported. These hypotheses were supported for FAA and HRV, but not for cortisol reactivity. Cortisol reactivity may have a divergent pattern of association across dyads for several reasons. First, Studies 1 and 2 revealed that AUCg to a specific stressor may not capture the same conceptual regulatory processes as resting-state FAA and HRV. This difference may be exacerbated when examining dyadic associations, as AUCg is the only measure across physiological indices that used different tasks for mothers and infants. Next, prior research suggests that cortisol reactivity differs across maternal symptoms for adults, such that reactivity may be blunted in lifetime history of MDD but is elevated in times of high life stress, though each of these symptom profiles may relate to parasympathetic withdrawal in infants (Burke et al., 2005; Rash et al., 2015).

The current results offer preliminary support for the hypotheses that FAA and HRV are heritable markers of risk for depression. These indices, particularly FAA and LF-HRV, demonstrated patterns of intergenerational transmission, negative associations with current maternal depression, and no evidence of depression moderating dyadic associations. These results also support the ECI conceptual model of depression vulnerability; however, it is notable that the pattern of effects across all infant physiological regulation indicators (i.e., including the pattern of

effects seen for AUCg, though not significant) and current maternal depression mirrors previous research that found support for the ACM model. Specifically, Nederhof and colleagues (2015) demonstrated that youth with high cortisol reactivity and low RSA reactivity had the largest increases in internalizing symptoms across time. Thus, the current results are inconclusive and should be interpreted with caution.

STUDY 4: SUPPLEMENTAL ANALYSIS

The proposed analyses included investigation of current maternal depressive symptoms with regard to regulation across neural, autonomic, and HPA axis domains and intergenerational transmission of depression risk; however, the initial analyses did not take into account maternal anxiety symptoms. Previous research investigating psychophysiological regulation in adults and transmission of risk from parent to offspring has demonstrated the importance of investigating comorbid anxiety alongside depressive symptomatology. For instance, several studies have demonstrated that depression with comorbid anxiety produces dampened associations with FAA compared to those found in pure depression diagnoses (Bruder et al., 1997; Kentgen et al., 2000; Thibodeau et al., 2006). This pattern has been seen across neurophysiological measures of emotion and reward processing such that depression and anxiety have separate and opposing effects on reactivity (MacNamara, Kotov, & Hajcak, 2016; Proudfit et al., 2015; Hajcak Proudfit, Bress, Foti, Kujawa, & Klein, 2014; Weinberg, Perlman, Kotov, & Hajcak, 2016). This has muddied the literature to the point that there has been a call for anxiety to be included as a measure in future studies investigating depression across affective neuroscience generally (Tracy, Klonsky, & Hajcak Proudfit, 2014) and those investigating FAA specifically (Jesulola, Sharpley, Bitsika, Agnew, & Wilson, 2015). A similar plea has been seen in investigations regarding transmission of depression risk, as family history of anxiety blunts associations across maternal history of depression and infant neurophysiological risk markers (Kujawa et al., 2016). The blunting of associations in comorbid cases may vary across physiological systems, however, as reduced RSA seems to be equivalent across MDD, generalized anxiety disorder (GAD), and MDD/GAD comorbid presentations (Kircanski, Waugh, Camacho, & Gotlib, 2016).

The aim of Study 4 is to investigate the role of maternal anxiety across the associations between depression and physiological regulation in mothers and infants. Specifically, across the first three studies, effects were small to moderate and largely non-significant. Based on previous research indicating blunted effects in comorbid depression and anxiety and at times the directly opposing effects of anxiety on physiological markers of risk, I hypothesized that controlling for current maternal anxiety symptoms would isolate the unique effects of depression. Data analyses across Studies 1-3 were re-ran with the addition of controlling for current maternal anxiety. Controlling for current anxiety symptoms across analyses first allowed me to explore associations

between maternal depression and maternal physiological regulation across systems, then maternal depression and infant physiological regulation, and finally the associations between maternal and infant physiological regulation controlling for both maternal depression and anxiety.

Method

Participants, procedures, clinical assessment, physiological assessment, and data recording and processing were equivalent to those described across Studies 1-3. Data analysis differences are described in turn below.

Data Analysis

Of note, supplemental analyses were computed using Mplus computational software (Muthen & Muthen, 1998-2007) so that missing data could be handled according to best practices (Newman, 2014). Specifically, the full information maximum likelihood (FIML) missing data routine was used—which utilizes all available data to calculate parameter estimates and standard errors using a model-based approach—rather than multiple imputation, which is not suggested when partial respondents make up greater than 10% of the sample (Newman, 2014). The maximum likelihood robust indicator was used across all analyses.

Study 1 sought to assess how the coordination, or lack thereof, of regulation across physiological systems relates to depression. Based on the largely null results of Study 1, the literatures for each physiological indicator, the overarching ECI framework, and the literature regarding comorbid depression and anxiety presentations on physiological markers, I hypothesized that DASS-21 depression symptoms would be associated with blunted engagement across physiological measures (FAA, RSA, and AUCg), specifically when controlling for DASS-21 anxiety symptoms. In this analysis, DASS-21 depression scores were regressed onto all maternal physiological indicators, controlling for DASS-21 maternal anxiety scores.

Study 2 sought to assess the association between regulation across infant physiological systems and maternal depression. Based on the largely small effects found in Study 2, the literatures for each infant physiological indicator and maternal depression, and the literature regarding familial anxiety blunting effects related to intergenerational transmission of depression risk markers, I hypothesized that the associations between maternal DASS-21 depression

symptoms and blunted engagement across infant physiological measures (FAA, RSA, and AUCg) would be larger when controlling for maternal DASS-21 anxiety symptoms.

Study 3 sought to assess the intergenerational associations of the physiological indicators, as well as the role of depression in these associations. Based on the literatures for each infant physiological indicator and maternal depression, and the literature regarding familial anxiety blunting effects related to intergenerational transmission of depression risk markers, I hypothesized that physiological indicators would be related across mother and infant and that these associations would be larger when controlling for maternal DASS-21 anxiety symptoms. I was also interested in investigating physiological and symptom effects within the same regression models to explore if effects seen in the previous literature (e.g., maternal depression predicting infant physiology) are driven by the transmission of physiological regulation, maternal depressive symptoms explicitly, or a combination of both. In this analysis, four models were run such that each infant indicator (e.g., infant FAA) was regressed onto each matching maternal indicator (e.g., mother FAA), maternal DASS-21 depression, and maternal DASS-21 anxiety as simultaneous predictors. Maternal DASS-21 depression and anxiety symptoms were both included in the model in order to (1) examine if they offered unique information from the maternal physiological indicator and (2) control for these effects.

Results

With regard to adult physiological regulation, current maternal depression symptoms were regressed onto physiological indicators (FAA, HRV, and AUCg) controlling for current anxiety symptoms. I hypothesized that current DASS-21 depression symptoms would be associated with blunted engagement across physiological measures, specifically when controlling for current maternal DASS-21 anxiety symptoms. The regression model is available in Table 10. The model significantly predicted maternal DASS-21 depression symptoms; however, this was driven by DASS-21 anxiety symptoms. Maternal FAA, RSA, and cortisol reactivity did not significantly predict DASS-21 depression symptoms. In the hypothesized direction, both FAA and AUCg shared a small, negative association with DASS-21 depression. Contrary to hypotheses, RSA shared a small, positive, and non-significant association with current depression symptoms.

Table 10. Regression Predicting Current Maternal Depression Symptoms, Controlling for Anxiety

Outcome: Maternal DASS-21 depression symptoms	*B*	*SE (B)*	β	*p*
Mother FAA	-.06	3.44	.00	.987
Mother RSA	.45	.26	.15	.091
Mother AUCg	-.12	.28	-.05	.670
Maternal DASS-21 anxiety	.67	.13	.66	.000
	Overall R^2 *= .48*			.008

Note. Beta is STDYX standardization.

With regard to maternal depression and infant physiological regulation, maternal DASS-21 depression symptoms were regressed onto infant physiological indicators (FAA, HRV, and AUCg) controlling for maternal DASS-21 anxiety symptoms. I hypothesized that the associations between maternal DASS-21 depression symptoms and blunted engagement across infant physiological measures (FAA, HRV, and AUCg) would be larger when controlling for maternal DASS-21 anxiety symptoms. Here, HRV was operationalized as RSA and LF-HRV due to the significant associations found at the bivariate level. The regression models are available in Table 11. In the first model utilizing RSA to investigate HRV, the overall model significantly predicted maternal DASS-21 depression symptoms. Maternal DASS-21 anxiety shared a large, positive association with maternal DASS-21 depression. Moreover, two associations were also demonstrated in the hypothesized direction. Maternal DASS-21 depression and infant FAA shared a significant, negative association such that greater maternal depression symptoms were associated with less approach motivation in infants. Infant RSA shared an association in the same direction, indicating greater maternal depression symptoms were associated with less flexibility to environmental demands in infants, though this association was not significant in the current model. Lastly, contrary to hypotheses, maternal DASS-21 depression and infant AUCg shared a small, positive, and non-significant association. The model utilizing LF-HRV to operationalize HRV produced a parallel pattern of results. Infant LF-HRV shared a non-significant small, negative association with maternal DASS-21 depressive symptoms.

Table 11. Regression Predicting Current Maternal Depression Symptoms, Controlling for Anxiety

Outcome: Maternal DASS-21 depression	*B*	*SE (B)*	β	*p*
Infant FAA	-13.75	6.48	-.23	.045
Infant RSA	-.20	.55	-.07	.721
Infant AUCg	.23	.55	.09	.153
Maternal DASS-21 anxiety	.71	.13	.70	.000
	Overall R^2 = .51			.002
Outcome: Maternal DASS-21 depression	*B*	*SE (B)*	β	*p*
Infant FAA	-15.20	4.89	-.25	.004
Infant LF-HRV	-.82	.57	-.26	.140
Infant AUCg	.28	.18	.11	.171
Maternal DASS-21 anxiety	.64	.12	.64	.000
	Overall R^2 = .42			.046

Note. Beta is STDYX standardization.

With regard to dyadic associations across physiological systems, four regression analyses were conducted such that each infant physiological indicator was regressed onto the analogous maternal physiological indicator, maternal DASS-21 depression, and maternal DASS-21 anxiety. Across models, I hypothesized that physiological indicators would be related across mother and infant, that including maternal DASS-21 depression symptoms would not nullify associations, and that these associations would be larger when controlling for maternal DASS-21 anxiety symptoms. The regression models are available in Table 12. The first regression explored FAA associations and overall significantly predicted infant FAA. This model demonstrated that mother and infant FAA shared a moderate, positive, and significant association as hypothesized. Maternal DASS-21 depression also significantly predicted blunted FAA in infants. Of note, maternal DASS-21 anxiety significantly predicted larger FAA in infants, an effect directly opposing, and similar in size, to maternal DASS-21 depression. The regression model exploring RSA produced a similar pattern of results, though the overall model was non-significant. Mother and infant RSA shared a moderate, positive, and significant association as hypothesized. Maternal DASS-21 depression was also associated with reduced infant RSA, though this association was non-significant. As with FAA,

maternal DASS-21 anxiety had an opposing effect of similar magnitude to maternal DASS-21 depressive symptoms on infant RSA. Using LF-HRV to investigate HRV associations produced a significant model wherein mother and infant LF-HRV were moderately, positively associated and maternal DASS-21 depression was associated with reduced LF-HRV. Once again, maternal DASS-21 anxiety was positively associated with infant LF-HRV, though this effect was non-significant. The regression exploring cortisol reactivity produced disparate effects to those of HRV and FAA. Each of the associations were non-significant and in opposing directions to hypotheses. Specifically, mother and infant AUCg shared a small, negative association and maternal DASS-21 depression and infant AUCg shared a small, positive association. Maternal DASS-21 anxiety shared an association with infant AUCg of equal direction and magnitude as maternal DASS-21 depression and infant AUCg.

Table 12. Regressions Predicting Infant Physiological Measures, Controlling for Maternal Anxiety

Outcome: Infant FAA	*B*	*SE (B)*	β	*p*
Mother FAA	.13	.06	.31	.013
Maternal DASS-21 depression	-.01	.00	-.41	.011
Maternal DASS-21 anxiety	.01	.00	.39	.046
	Overall R^2 = .20			.050
Outcome: Infant RSA	*B*	*SE (B)*	β	*p*
Mother RSA	.37	.17	.33	.023
Maternal DASS-21 depression	-.05	.13	-.15	.660
Maternal DASS-21 anxiety	.05	.11	.13	.664
	Overall R^2 = .11			.267
Outcome: Infant LF-HRV	*B*	*SE (B)*	β	*p*
Mother LF-HRV	.32	.13	.41	.002
Maternal DASS-21 depression	-.16	.07	-.48	.028
Maternal DASS-21 anxiety	.06	.07	0.19	.332
	Overall R^2 = .29			.031
Outcome: Infant AUCg	*B*	*SE (B)*	β	*p*
Mother AUCg	-.13	.21	-.14	.489
Maternal DASS-21 depression	.04	.08	.10	.614
Maternal DASS-21 anxiety	.04	.14	.10	.758
	Overall R^2 = .05			.596

Note. Beta is STDYX standardization.

Interim Discussion: Study 4

The present study sought to investigate the role of current maternal anxiety in the associations amongst maternal depression and maternal physiological regulation, infant physiological regulation, and the dyadic associations of these processes. Together, the present series of analyses suggest that physiological regulation across systems—neural, autonomic, and the HPA axis—do not relate to current depression or anxiety symptoms in the present adult sample. However, current maternal depressive symptoms do relate to physiological regulation across neural and autonomic systems in infants, when controlling for current maternal anxiety symptoms. Across HRV models, it seems that sympathetic activity is particularly important to understanding the effects of maternal autonomic activity and depressive symptoms on infant autonomic activity. Moreover, infant dysregulation across neural and autonomic systems may represent overlapping associations with maternal depression, as infant FAA and LF-HRV each shared significant associations with current maternal depression only when assessed in separate models. Cortisol reactivity was not associated across mother and infant, and did not significantly relate to current maternal depression symptoms, suggesting further need for investigation of stress response associations. Finally, these analyses suggest that for neural and autonomic systems, maternal physiological regulation (i.e., FAA, RSA) and maternal psychopathology (i.e., depression symptoms) may serve as separate pathways in predicting infant physiological regulation. Moreover, current results support previous research indicating that consideration of maternal anxiety is crucial to identifying these effects.

STUDY 5: SUPPLEMENTAL ANALYSIS

The proposed analyses (i.e., Studies 1-3) included investigation of current depressive symptoms with regard to regulation across neural, autonomic, and HPA axis systems (FAA, HRV, and cortisol reactivity, respectively) and intergenerational transmission of risk; however, much of the past literature has either limited their investigations to samples that meet criteria for MDD (e.g., Burke et al., 2005) or explicitly demonstrated that environmental responsiveness relates to lifetime history or vulnerability to MDD above and beyond current depressive symptoms (Allen & Reznik, 2015; Allen, Urry, Hitt, & Coan, 2004; Kemp et al., 2010; Nusslock et al., 2011; Urry, Hitt, & Allen, 1999). This distinction is particularly important in investigating the effects of depression because MDD is a psychological disorder diagnostically defined by MDD episodes. MDD episodes are characterized by markedly increased symptoms and reduced functioning in comparison to individuals' routine functioning; these episodes last two weeks to one year for a majority of patients (American Psychiatric Association, 2013). Outside of MDD episodes, increases in current symptoms related to depression, anxiety, or stress may be caused by a multitude of non-specific factors, such as life stress. Thus, increases in symptoms across domains are not by definition indicative of MDD illness, and the vulnerability factors that predict illness may not relate to current symptoms.

The aim of Study 5 was to investigate physiological regulation across systems in mothers and infants using maternal lifetime history of MDD, rather than current maternal depressive symptoms. Specifically, across the first four studies, effects of maternal DASS-21 depression and maternal physiological regulation across systems were small and non-significant. Here, I hypothesized that adult physiological markers of depression vulnerability would share stronger associations with lifetime history of depressive illness (i.e., MDD diagnosis from the SCID-5) than current depressive symptoms (i.e., as measured by the DASS-21). The first four studies revealed moderate associations between current maternal depression and infant physiological markers of depression risk when controlling for current maternal anxiety, and reviewed why current maternal symptoms may differentially impact mother and infant physiological regulatory systems. In the current study, I hypothesized that maternal lifetime history of illness would have an analogous impact on infant physiological regulation insofar as regulatory patterns across systems may serve as markers for depression vulnerability. In the present study, data analyses across Studies 1-3 were

re-ran operationalizing depression as lifetime history of MDD instead of current depressive symptoms. Given the literature detailed above regarding the importance of considering comorbid anxiety presentations, the current study also controlled for maternal lifetime history of any anxiety disorder.

Method

Participants, procedures, clinical assessment, physiological assessment, and data recording and processing were equivalent to those described across Studies 1-3. Data processing differences are described in turn below.

Data Analysis

These supplemental analyses were computed using Mplus computational software (Muthen & Muthen, 1998-2007) so that missing data could be handled according to best practices (Newman, 2014). Specifically, the full information maximum likelihood (FIML) missing data routine was used—which utilizes all available data to calculate parameter estimates and standard errors using a model-based approach—rather than multiple imputation, which is not suggested when partial respondents make up greater than 10% of the sample (Newman, 2014). The maximum likelihood robust indicator was used across all analyses.

Study 1 sought to assess how the coordination, or lack thereof, of regulation across physiological systems relates to depression. Based on the literatures for each physiological indicator, the overarching ECI framework, and the largely null results of Study 1, I hypothesized that lifetime history of MDD (as measured by the SCID-5), rather than current depressive symptoms (as measured by the DASS-21), would be associated with blunted engagement across physiological measures (FAA, HRV, and AUCg). Of note, lifetime MDD was operationalized as number of MDD episodes across the lifetime, in order to allow for statistical control of lifetime anxiety disorder diagnoses.[7] While this decision was made due to the nature of the current sample,

[7] In the current dataset, 83% of lifetime anxiety disorder cases were nested within lifetime MDD cases (making up 38.46% of the lifetime MDD cases), and thus count variables had to be substituted in order to investigate both effects simultaneously. With regard to the distribution of MDD episodes, one value was determined to be a statistical outlier. The SCID-5 also allows for a "99" designation in the case that MDD episodes are "too numerous or indistinct to count" (First et al., 2015). In each case, these values were indicated as missing in order to conservatively estimate the effect of MDD episodes. Further, this variable was not correlated with age, $r = .08$, $p = .671$.

it is consistent with previous work that has demonstrated that FAA is likely a marker of vulnerability to MDD rather than a marker of current MDD state or current depressive symptoms. Indeed, several studies have demonstrated that current MDD and remitted MDD samples share equally blunted FAA in comparison to healthy controls (Bagley et al., 2011; Gotlib et al., 1998). Thus, number of lifetime MDD episodes is one way to examine the effects of lifetime illness, and vulnerability to MDD episodes in particular, instead of using a binary variable. In the first analysis, number of maternal lifetime MDD episodes was regressed onto maternal physiological indicators, controlling for SCID-5 maternal lifetime anxiety disorders, as simultaneous predictors. In the regression analyses, HRV was operationalized specifically as RSA.

Study 2 sought to assess the association between regulation across infant physiological systems and maternal depression. Study 4 revealed that infant FAA and HRV are both negatively associated with maternal DASS-21 depression symptoms, when controlling for maternal DASS-21 anxiety symptoms. I hypothesized that maternal lifetime MDD episodes would likewise be associated with blunted regulation in infants across indicators when controlling for SCID-5 maternal lifetime anxiety disorders. In this analysis, maternal lifetime MDD episodes were regressed onto infant FAA, HRV, and AUCg while controlling for SCID-5 maternal lifetime history of anxiety disorders as simultaneous predictors. As in Studies 2 and 4, this model was first ran with infant HRV operationalized as RSA and then as LF-HRV.

Study 3 sought to assess the intergenerational associations of the physiological indicators, as well as the role of depression in these associations. Study 4 revealed that dyads shared moderate associations across neural and autonomic systems, but not the stress response system, and that maternal DASS-21 symptoms of depression and anxiety had separate and opposing effects on infant physiological regulation. Based on these results, I hypothesized that neural and autonomic physiological indicators would be related across mother and infant. Further, I hypothesized that maternal lifetime history of MDD would separately predict infant physiological regulation when controlling for maternal lifetime history of anxiety disorders. In this analysis, four models were ran such that each infant indicator (e.g., infant FAA) was regressed onto each matching maternal indicator (e.g., mother FAA) and maternal lifetime MDD episodes, controlling for SCID-5 maternal lifetime anxiety disorders.

Results

With regard to adult physiological regulation across systems, a regression analysis was utilized to assess the role of lifetime MDD while controlling for the presence of lifetime anxiety disorders. I hypothesized that number of lifetime MDD episodes would be associated with blunted regulation across physiological measures (FAA, HRV, and AUCg). As predicted, each of the maternal physiological measures was negatively associated with maternal lifetime MDD; however, only the AUCg and lifetime MDD episode association was significant (Table 13). Of note, SCID-5 lifetime anxiety disorders also shared a small, though non-significant association with lifetime MDD.

Table 13. Regression Predicting Mother Lifetime MDD Episodes, Controlling for Lifetime Anxiety Disorders

Outcome: Maternal lifetime MDD episodes	*B*	*SE (B)*	β	*p*
Mother FAA	-2.87	5.63	-.14	.562
Mother RSA	-.08	.28	-.04	.776
Mother AUCg	-.48	.31	-.28	.018
Maternal lifetime anxiety disorders	1.02	.57	.29	.120
	Overall R^2 *= .17*			.072

Note. Beta is STDYX standardization.

With regard to maternal MDD and infant physiological regulation, two regressions were utilized to assess the associations between regulation across infant physiological systems and maternal lifetime MDD episodes, controlling for SCID-5 maternal lifetime anxiety disorders (Table 14). I hypothesized that mothers' number of lifetime MDD episodes would be associated with blunted regulation across physiological measures in infants. Two models were run such that HRV was first operationalized as RSA and then as LF-HRV. In the first model, number of maternal lifetime MDD episodes negatively predicted infant FAA, such that maternal depression was associated with blunted FAA in infants as hypothesized, though the effect was non-significant. Infant RSA and AUCg also demonstrated effects in the same, hypothesized direction, though were non-significant. In the second model, the overall model was significant and the effect patterns were

analogous to the first—except infant LF-HRV shared a significant and moderate, rather than small, association with maternal lifetime MDD.

Table 14. Regression Predicting Mother Lifetime MDD Episodes, Controlling for Lifetime Anxiety Disorders

Outcome: Maternal lifetime MDD episodes	*B*	*SE (B)*	β	*p*
Infant FAA	-10.68	11.63	-.23	.266
Infant RSA	-.51	.56	-.24	.294
Infant AUCg	-.03	.16	-.02	.864
Maternal lifetime anxiety disorders	1.34	.58	.38	.042
	Overall R^2 = .13			.173
Outcome: Maternal lifetime MDD episodes	*B*	*SE (B)*	β	*p*
Infant FAA	-10.10	.46	-.20	.117
Infant LF-HRV	-1.04	.65	-.41	.012
Infant AUCg	-.05	.13	-.02	.716
Maternal lifetime anxiety disorders	1.69	.43	.45	.001
	Overall R^2 = .33			.013

Note. Beta is STDYX standardization.

With regard to dyadic associations across physiological systems, four regression analyses were used to assess intergenerational associations of the physiological indicators, as well as the role of maternal lifetime MDD episodes and SCID-5 anxiety disorders in these associations. I hypothesized that physiological indicators would be related across mother and infant. Further, I hypothesized that maternal lifetime history of MDD and SCID-5 anxiety disorders would separately predict infant physiological regulation in opposing directions to each other. Regression models are available in Table 15. For FAA, the overall model was non-significant; of note, while each association was non-significant, the associations were each in the hypothesized direction.

Table 15. Regressions Predicting Infant Physiological Measures, Controlling for Maternal Lifetime Anxiety Disorders

Outcome: Infant FAA	*B*	*SE (B)*	β	*p*
Mother FAA	.10	.06	.23	.083
Maternal lifetime MDD episodes	.00	.00	-.12	.236
Maternal lifetime anxiety disorders	.02	.01	.20	.229
	Overall R^2 = .12			.244
Outcome: Infant RSA	*B*	*SE (B)*	β	*p*
Mom RSA	.33	.16	.30	.046
Maternal lifetime MDD episodes	-.06	.07	-.13	.381
Maternal lifetime anxiety disorders	.54	.32	.32	.069
	Overall R^2 = .19			.104
Outcome: Infant LF-HRV	*B*	*SE (B)*	β	*p*
Mom LF-HRV	.36	.12	.46	.000
Maternal lifetime MDD episodes	-.20	.03	-.52	.000
Maternal lifetime anxiety disorders	.34	.22	.23	.085
	Overall R^2 = .37			.004
Outcome: Infant AUCg	*B*	*SE (B)*	β	*p*
Mom AUCg	-.13	.16	-.14	.354
Maternal lifetime MDD episodes	-.04	.05	-.08	.300
Maternal lifetime anxiety disorders	-.30	.22	-.16	.056
	Overall R^2 = .05			.297

Note. Beta is STDYX standardization.

Mother and infant FAA shared a small, positive association. Maternal lifetime MDD episodes also related to blunted infant FAA and SCID-5 maternal lifetime history of anxiety disorders shared a positive association with infant FAA. For both measures of infant HRV (i.e., RSA and LF-HRV), mother and infant HRV shared significant moderate, positive associations. Mothers' number of lifetime MDD episodes related to blunted HRV in both models; however, this effect was large and significant for LF-HRV and non-significant for RSA. Again, mothers' SCID-5 lifetime anxiety disorders shared positive, though non-significant, associations with infant HRV indices. For cortisol reactivity, mother and infant AUCg measures shared a small, negative and non-significant association. Infant AUCg also shared non-significant, small, and negative associations with mothers' SCID-5 lifetime MDD and anxiety disorders.

Interim Discussion: Study 5

Together, the present series of analyses suggest that adult physiological regulation across systems—neural, autonomic, and HPA axis—may relate to lifetime history of MDD more so than to current depressive symptoms in adults. As demonstrated in Study 4, anxiety continues to play a role in understanding associations between depression and physiological regulation. When looking at the effects of maternal MDD on infant regulatory systems, MDD and anxiety disorders have directly opposing effects on neural and autonomic processes. For infant hormonal regulation, maternal MDD and anxiety disorders produced small, analogous effects.

In the current study, lifetime MDD was operationalized as number of MDD episodes across the lifetime. While previous work has demonstrated that FAA is a marker of vulnerability to MDD rather than a marker of state MDD (Allen et al., 2004; Bagley et al., 2011; Gotlib et al., 1998), it is important to note that the effect of number of lifetime MDD episodes is not equivalent to the mere presence of lifetime MDD. Indeed *vulnerability* toward MDD is not well defined in the literature. The count variable used here serves as one way to operationalize propensity to experience depressive episodes across the lifetime; however, it also misses key information in characterizing MDD, such as information regarding age of onset, MDD subtype, or lifetime chronicity of MDD, all of which are likely important to characterizing the physiological processes in MDD (Klein, 2008; Quinn, Rennie, Harris, & Kemp, 2014; Shankman, Klein, Tenke, & Bruder,

2007; Shankman & Rose, 2006). Thus, future work should examine each of these MDD characteristics, ideally longitudinally rather than retrospectively, to disentangle these effects.

Furthermore, two of the current regression models were constructed with maternal lifetime MDD episodes as the outcome variable such that mother and infant physiological indices predicted maternal lifetime MDD. The models were constructed in this way to remain consistent with the analyses conducted in Studies 1 and 2, and this model configuration continued to serve the purpose of investigating associations between each physiological indicator and depression while controlling for the other physiological indicators included in the model. However, because of the regression framework, a shortcoming of this configuration is the suggestion of using current physiological functioning to predict past illness. Of note, the current analyses were used and interpreted to assess associations rather than literal prediction given the temporal associations amongst the variables included. An alternate model configuration would be to run one model for each mother and infant physiological indicator wherein that indicator is regressed onto maternal lifetime MDD episodes, maternal anxiety disorders, and the remaining mother or infant physiological indices.

While adult physiological regulation across systems was related to lifetime MDD and not current depression symptoms, the distinction of lifetime illness versus current symptoms is not as clear when examining infant physiological regulation. Previous research has indicated that adult neural and autonomic regulatory patterns are associated with lifetime illness rather than current symptom severity (Allen & Reznik, 2015; Allen et al., 2004; Bagley et al., 2011; Burke et al., 2005; Kemp et al., 2010; Nusslock et al., 2011; Urry et al., 1999); however, work with infants has suggested that maternal psychosocial functioning throughout pregnancy and early childhood play a role in the development of offspring physiological regulation (Diego et al., 2006; Gustafsson et al., 2018; Wen et al., 2017). The disparate effects of maternal lifetime illness and maternal current symptoms may also explain the divergent associations of infant cortisol across Studies 4 and 5. When looking at maternal current symptoms, infant AUCg shares small, positive associations with both depression and anxiety. This supports previous work demonstrating that high maternal life stress relates to larger cortisol reactivity and infant parasympathetic withdrawal (Rash et al., 2015). However, when examining maternal lifetime history of illness, infant AUCg shows a withdrawal pattern, though small and non-significant, more similar to the cortisol reactivity withdrawal pattern

seen in adults with MDD in the current study and in previous meta-analytic work (Burke et al., 2005).

GENERAL DISCUSSION

The current series of studies utilized multiple physiological measures—EEG, ECG, and salivary cortisol—to investigate competing theoretical models from separate lines of research to investigate regulatory patterns in depression and the intergenerational transmission of these patterns. For adults, results demonstrated that physiological regulatory patterns are more related to lifetime history of depressive illness than current symptom severity. In contrast, results demonstrated that infant regulatory patterns are perhaps impacted by both current maternal symptoms and maternal lifetime history, and the effects are strongest for current symptoms. For both adults and infants, results demonstrated that accounting for concurrent anxiety is essential to understanding regularity patterns, as anxiety—both current and lifetime—seems to have an opposing effect to depression. Lastly, perhaps the most noteworthy findings are those that demonstrate the associations between neural and autonomic systems across mother and infant. Each of these findings, as well as support for the ECI and ACM conceptual models of physiological regulation, are discussed in turn below.

The Pathophysiology of Depression in Adults

In adults, FAA and RSA share a moderate association, indicating that approach motivation and parasympathetic flexibility to environmental demands are associated within individuals. Indeed, both reduced FAA and RSA have been conceptualized as withdrawal from the surrounding environment and decreased emotion regulation. This association, along with the pattern of effects found with lifetime MDD, wherein indices of FAA, RSA, and AUCg shared negative associations with MDD episodes, lends support for the ECI model. Specifically, this pattern further replicates the current evidence for ECI, which is primarily composed of self-report and autonomic physiological measures, with increasing support from neurophysiological studies (Rottenberg & Hindash, 2015). Investigations of the HPA axis have so far eluded this literature, however. To date, there is one meta-analysis on HPA functioning in depression that provides preliminary support for ECI (i.e., blunted cortisol reactivity related to depression); however, this effect was found only in severely depressed individuals (Burke et al., 2005). Replication of this finding in the current Study 5 may partially be driven by the use of MDD episodes as the indicator of illness rather than the

straightforward MDD diagnosis distinction, as this variable may serve as an imperfect proxy for severity.

In the present series of studies, cortisol reactivity was not associated with either FAA or HRV. These null findings may be indicative of the experimental procedures in the present study; FAA and RSA were both collected during the resting-state task, and AUCg was in response to an emotional press. However, previous studies have utilized resting-state and stressor tasks to measure FAA and cortisol reactivity, respectively, and found disparate findings from the present studies. For example, Quadflieg and colleagues (2015) found that enhanced resting-state FAA was associated with decreased cortisol reactivity to a stressor, indicating that approach motivation may modulate the stress response in healthy controls (Quaedflieg, Meyer, Smulders, & Smeets, 2015). When looking at these associations within the context of depression, the present pattern of results also seems to support the ECI model—lifetime history of MDD is associated with blunted FAA, RSA, and AUCg. These effects indeed replicate previous work demonstrating substantial support for ECI (Rottenberg & Hindash, 2015). These results also contrast the results of previous work wherein high cortisol reactivity *and* low RSA values prospectively predicted increases in internalizing difficulties in adolescent boys (Nederhof et al., 2015). However, there are several differences across these studies that highlight the need for further investigation. First, Nederhof and colleagues (2015) demonstrated that interactions amongst physiological indicators, and not main effects, predicted changes in symptoms over time. The main study investigated only main effects due to power constraints; however, future analyses with this dataset will use Bayesian structural equation modeling to allow for path investigation with small samples. Second, Nederhof and colleagues (2015) found that this effect was specific to adolescent boys, while the present study investigated patterns in adult women. It will be pertinent for future studies to investigate patterns of regulation across physiological systems in a large, longitudinal study to further investigate both developmental and sex differences in allostatic load and risk for internalizing psychopathology. Of note, according to the meta-analysis conducted by Burke and colleagues (2005), participants with mild MDD also demonstrated higher cortisol reactivity—the present ECI pattern was only found in subjects with severe MDD.

Intergenerational Transmission of Physiological Regulation and Risk for Depression

Previous work indicates that physiological regulation extends beyond markers of depression in adults to also capture markers of risk much earlier in the lifespan. A majority of this work has been accumulated by examining physiological indices in infants either with or without risk for depression according to maternal depression status. As in the adult literature, these studies have primarily focused on one physiological system at a time, leaving it unclear whether ECI or ACM theoretical models best explain early risk. The present series of studies replicated prior work that maternal depressive symptoms, particularly current symptoms, relate to neural and autonomic regulation in infants. Results revealed that dysregulation across neural and autonomic systems may represent overlapping risk factors, as FAA and HRV indices each shared significant associations with current maternal depression only when assessed in separate models. Cortisol reactivity was found to demonstrate a disparate pattern in relation to mothers' cortisol reactivity, maternal depressive symptoms, and maternal anxiety symptoms, and was not associated with FAA or HRV indices within infant participants, suggesting that this measure represents a separate process that is differentially impacted by mothers' life stress and lifetime MDD.

Insomuch as maternal depression relates to infant physiological regulatory patterns, the present studies were interested in examining the association of physiological regulation between mother and infant as the explanatory mechanism. There was support for intergenerational transmission of physiological regulation across neural and autonomic systems—mother and infant FAA shared a moderate association, as did mothers and infants on all HRV indices (RSA, LF-HRV, and HRV ratio). Mothers and infants did not relate on cortisol reactivity. These intergenerational associations did not fully account for intergenerational risk of depression, however, as maternal regulation and maternal depression were found to each significantly predict infant regulation as simultaneous predictors. These effects were most pronounced for FAA and LF-HRV models, indicating neural and sympathetic systems are particularly relevant to the intergenerational transmission of risk for depression across mothers and infants.

While an aim of the current studies was to examine risk for depression in infants, it is important to note that risk is only captured via maternal symptomatology in the current study. While depression does have a considerable heritability factor (Sullivan, Neale, & Kendler, 2000) and thus maternal status does serve as a risk factor for infants, a prospective longitudinal design is needed to better understand the predictive power of pathophysiological processes measured in

infancy and depression risk. Future analyses with the present sample will examine the reliability of these physiological measures over time, as data collection continues. Future investigations should also include assessments of emotion and behavior processing and regulation, internalizing and externalizing symptoms, and disorder onset to further examine the associations amongst regulation across physiological systems, familial risk, and concurrent functioning.

Theoretical Underpinnings of the Pathophysiology of Depression and Depression Risk

Taken together, consideration of both the current studies' results and the previous literature is needed to evaluate the viability of both the ECI and ACM theoretical frameworks. Indeed, the current studies and previous literature alike provide support for each. Figure 3 presents a conceptual reference for the following evaluation of these frameworks, wherein a theoretically intertwined developmental model is discussed. First, the ACM postulates that individuals develop physiological responses and regulatory patterns based on the components needed for success in the environment. Early in the lifespan, the results of current Studies 2, 3, and 4 suggest that infants of mothers with depression demonstrate dysregulation across systems—blunted approach motivation and flexibility to environmental demands (as measured via EEG/ERP and HRV) and enhanced stress responses (as measured by cortisol reactivity). These associations replicate previous work in newborns, infants and children, and adolescents at risk for depression (Buss et al., 2003; Diego et al., 2004; Nederhof et al., 2015; Peltola et al., 2014; Rash et al., 2015). These associations have also been supported in the literature with regard to both risk for depression and mild depression in adults (Allen & Reznik, 2015; Licht et al., 2008; Proudfit et al., 2015). This pattern of dysregulation across systems supports the ACM, and is specifically most reminiscent of the Type III Vigilant or Vigilant-Withdrawn calibration of stress responsivity physiological profile postulated by the ACM (Del Giudice et al., 2011). At this stage, burdened allostatic load—that is, bodily fatigue as a result of dysregulation across physiological systems—fits the pattern across systems. Of note, however, is how ECI patterns are also present in this model, as FAA and HRV indices indicate that individuals are showing a tendency to withdraw from the environment.

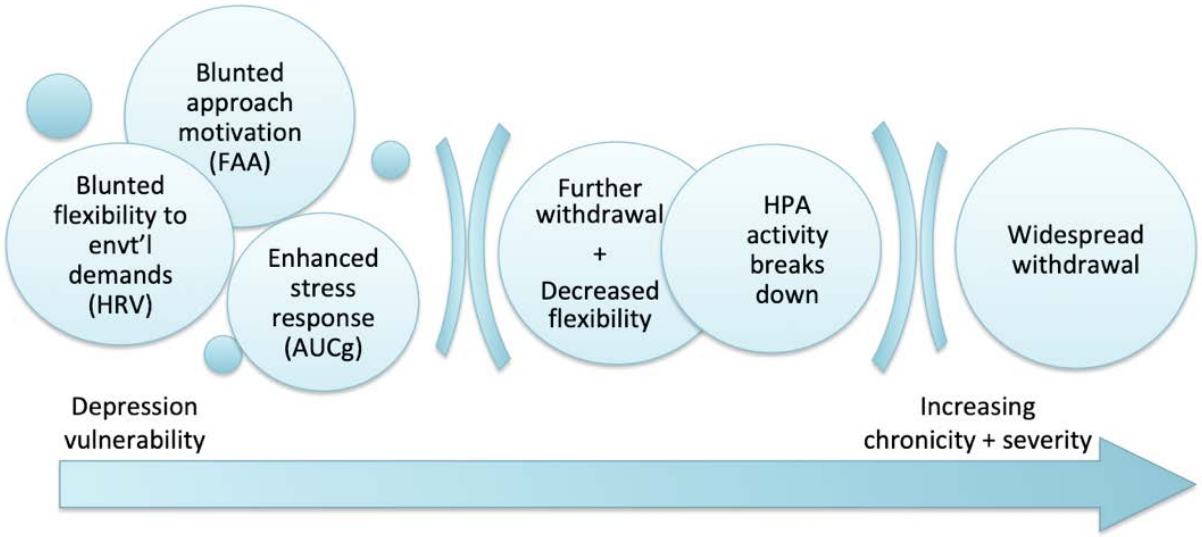

Figure 3. Depiction of proposed theoretical model wherein ACM and ECI exist along a developmental continuum.

This withdrawal pattern takes prominence in Study 5 of the present series of studies. In Study 5, greater number of lifetime MDD episodes is associated with blunted cortisol reactivity. This result supports the meta-analytic finding that severe MDD is characterized by reduced, rather than enhanced, HPA response (Burke et al., 2005). Thus, it seems that HPA activity breaks down with increased depression severity, and perhaps an extended developmental approach to the pathophysiology of depression is most appropriate. Following Figure 3, it seems that growing allostatic load (i.e., dysregulation across neural, autonomic, and HPA systems) may relate to depression vulnerability; and as symptom onset occurs, the allostatic load continues to increase, until the system breaks—leading to widespread withdrawal in severe cases. The widespread withdrawal at the severe end of the spectrum is consistent with ECI, and is supported by the broader literature of severe depression in adults (Allen & Reznik, 2015; Burke et al., 2005; Kemp et al., 2010). In this way, ACM and ECI models are not opposing insomuch as different stages of a developmental process. Assessing the two primary dimensions of MDD, severity and chronicity, may contribute to the understanding of what leads to complete breakdown across systems (Klein, 2008). Future investigations, which include large cohorts assessed across physiological systems over time, are needed to further clarify this plausible developmental model of the pathophysiology of depression.

Broad Themes in Examining the Pathophysiology of Depression

Across the proposed and supplemental analyses, two predominant themes emerge in investigating the pathophysiology of depression and early risk. First, current symptoms and lifetime history of disorders relate to physiological regulation differently. For adults, regulatory patterns diverged across associations with either current symptoms or lifetime history of illness. For example, FAA shares a small, negative association with lifetime MDD but a near-zero association with current depressive symptoms. This replicates previous work indicating that dispositional approach motivation, measured via FAA, relates to risk and lifetime history of MDD more so than current symptom status (Allen & Reznik, 2015; Allen et al., 2004). In the current studies, RSA shared a small, positive association with current symptoms and a small, negative association with lifetime MDD episodes. This pattern also replicates previous work demonstrating that current and lifetime history of depression differently relate to RSA (Bylsma, Salomon, Taylor-clift, Morris, & Rottenberg, 2014). Bylsma and colleagues (2014) emphasize, however, that

investigations comparing participants with current and remitted MDD should include both baseline and stressor induced measurements of RSA, and RSA reactivity best separates current from remitted MDD cases.

Second, anxiety symptoms and diagnoses relate to physiological regulation via directly opposing effects. This pattern was seen across the vast majority of models—including those assessing neural, autonomic, or HPA regulation and those examining current or lifetime history of symptoms. This pattern has been demonstrated in the literature (Bruder et al., 1997; Kentgen et al., 2000; MacNamara et al., 2016; Mathersul et al., 2008; Proudfit et al., 2015; Hajcak Proudfit et al., 2014; Thibodeau et al., 2006; Weinberg et al., 2016), and the current series of studies support the widespread call for disentangling internalizing psychopathology in this way in affective science (Tracy et al., 2014). A limitation to the current investigation is the nested nature of depression and anxiety diagnoses, further exacerbated by the high associations between current depression, anxiety, and stress symptoms. In fact, all GAD cases in the present sample were nested within MDD cases, making up approximately one third of the MDD subsample. Looking across anxiety disorder diagnoses, 83% were nested within MDD cases, making up 38.46% of the MDD sample. This limitation is reflective of the significant comorbidity and overlap in symptom presentations between MDD and GAD (Krueger & Markon, 2006; Moffitt et al., 2007). Future investigations could employ a strategic sampling strategy such that the effects of MDD and anxiety disorders could be disentangled across cases rather than solely statistical control for pure MDD or pure anxiety effects.

Conclusion

This series of studies have paved the way for future investigations to consider the importance of a psychophysiological battery of assessments to quantify pathophysiology patterns in depression. Results suggest that lifetime history of MDD is associated with blunted approach motivation across indicators for adults. Moreover, current maternal depressive symptoms played a larger role in determining infant physiological flexibility than did lifetime history of MDD, though the direction of effects were analogous for neural and autonomic measures. These patterns in conjunction with the literature suggest a developmental model to physiological regulation in MDD that encompasses both ACM and ECI frameworks. Results also suggested that the transmission of risk from mother to infant occurs via two distinct pathways—the first such that

dispositional regulation patterns are passed from mother to infant (i.e., FAA and HRV are moderately associated within dyads), and a second wherein maternal depression affects infants' physiological regulation. Consistent with prior work, all of these associations were strongest when controlling for anxiety. While further investigation is needed, the current studies offer insight into the pathophysiology of depression and its permeability across the lifespan.

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